Digital drug screening to detect falsified, expired and recalled medicines

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Abstract

Falsified medicines are a global health and pharmaceutical sector issue which affect supply chains in low, middle and high-income countries. There are many methods to identify substandard and falsified medicines. However, the European Union has introduced the Falsified Medicines Directive (FMD) to combat this problem. This directive requires the majority of all prescription-only medicines to be serialised, risk-based verified at wholesaler level and decommissioned at the end of the supply chain at a healthcare facility; using digital medicine screening technology (DMST) often referred to as medicines authentication technology.

This thesis implemented a DMST into a live hospital environment for use by healthcare professionals. This thesis looked at the technical and operational effectiveness of the proposed digital solution in a hospital, gained user consensus on the strengths and limitations of the hospital DMST and implemented technological change to understand if the proposed changes demonstrated a quantitative or qualitative benefit. This thesis explains how the health information technology (HIT) intervention was perceived by the users and draws on literature to explain the observed results. This thesis involved the development and testing of a mobile app based DMST which could be used by public for the verification of medicines. This thesis involved a sample of social media users to gain an understanding of the consumer-based medicine verification concept, its limitations, and its opportunities from a convenience sample cohort.

A DMST in a hospital environment can work effectively in practice. However, some factors such as DMST offline instances, poor compliance to the DMST alerts and poor staff engagement remain a risk for this solution. It is established that 'active' alerts, such as an audio alert can improve adherence to policy (detection rates) and that staff-led technology improvements have a positive impact on technology compliance. There is also a consumer appetite for a mobile DMST app, and although some consumers are happy to share their data, this cohort would prefer if a hospital or University controlled the data generated by the app due to concerns relating to data management. This thesis has generated evidence to support the development of DMST systems for hospitals and mobile phone users.

Keywords: Falsified, Substandard, Counterfeit, Medicine, Pharmaceutical Supply Chain, Management, Global Health, Health Policy, Operations, Organisational Behaviour, Implementation, Health Information Technology, Healthcare Information Technology Alerts, Digital Technology, Health Information Alerts and Drug Screening.

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Frequently used Acronyms and Abbreviations

1D	One Dimensional
2D	Two Dimensional
ADR	Absolute Detection Rate
CA	Computer Calendar Alerts
CD	Controlled Drugs
CHTSU	Central Hospital Trust Storage and Distribution Unit
DDST	Digital Drug Screening Technology
DR	Delegated Regulation
DSCSA	Drug Supply Chain Security Act
EMVS	European Medicines Verification System
EMVO	European Medicines Verification Organisation
EPR	Electronic Prescription Record
FAS	Fridge Alert System
FMD	Falsified Medicines Directive
GS1	Global Standard One
GTIN	Global Trade Item Number
HIC	High Income Country
HIT	Health Information Technology
JKK	Jikotei Kanketsu
LMIC	Low and Middle-Income Country
MAS	Medicines Authentication System
MAT	Medicines Authentication Technology
NMVO	National Medicines Verification Organisation
NMVS	National Medicines Verification System
OAR	Operational Authentication Rate
ODR	Operational Detection Rate
PMR	Patient Medicines Record
RFID	Radio Frequency Identification
RR	Response Rate
SF	Substandard and Falsified
SNI	Standardised Numerical Identifier
UI	Unique Identifier
UK	United Kingdom
US	United States of America
WHO	World Health Organisation

Foreword

Governments, pharmaceutical companies and charities spend millions annually to fund clinical trials in an attempt to develop vaccines, biologicals and pharmaceuticals to tackle some of the most dangerous diseases that face our planet. Doctors, pharmacists and nurses deal with these medicines on a daily basis, prescribing, supplying and administering these products to ease pain, prolong life expectancy and cure disease. However, some of these medicines are substandard or falsified. Countries around the world have introduced legislation which requires the serialisation of medicines by manufacturers. This will help healthcare professionals to verify or track and trace medicines to ensure that falsified medicines are identified and investigated. This thesis reviews the prevalence of falsified medicines, the terminology, regulations and laws governing medicine falsification, the methods to detect falsified medicines, and public health campaigns to raise awareness of this international problem. This thesis then investigated the Falsified Medicines Directive (FMD) digital drug screening approach and how the FMD and the mandated screening approach impacts hospital pharmacy practice. The technical and operational effectiveness of the drug screening approach is assessed, and pharmacy staff are surveyed using the Delphi method approach, to identify improvements for the proposed technology. The 'most important' suggestion as identified by the participants, was an active audio alert, is implemented and qualitative interviews identify the effectiveness of alerts in the workplace and considerations for building technologies which use health information technology alerts. The thesis

then finishes with a survey based on mobile phone digital drug screening and consumer perception of safe medicine supply.

The outcomes of this thesis relate directly to the implementation of the FMD in pharmacy practice but also provides wider learning associated with other screening technologies. In terms of pharmacy practice this thesis answers key questions relating to the proposed drug screening technology. There are also learnings in chapter six which will contribute to theory on innovation with ownership (JKK), how health information technologies are developed in the future, and learning which may influence future research in the area of falsified medicines purchased online.

1.0: A Literature Review of Medicine Falsification Regulations and Approaches to Protect Public Health

The Prevalence of Falsified and Counterfeit Medicine Internationally

Medicine falsification is a problem that is often perceived to affect high-value medicines in low and middle-income countries (LMICs). However, the trade of counterfeit, falsified or substandard medical products is a lucrative industry affecting all medicines and countries across all levels of development (**Figure 1.0**). In France in 2013, 1.2 million doses of falsified aspirin, a well-known low-cost medicine, without an active ingredient were seized (1). In the USA in 2012, falsified Avastin® (bevacizumab) a high-cost drug lacking active ingredient was discovered, affecting 19 medical practices (2-3). According to the pharmaceutical security institute over the past five years, there has been a 56% increase in the global incidence of counterfeiting, illegal diversion and theft incidents with 2017 seeing the highest levels to date (4). This upward trend can be seen in the UK supply chain also where 11 cases of falsified medicines were detected over a 11year period (2001-2011) (5). The direct effect of medicine falsification includes deterioration of medicine quality and therefore poor patient outcomes, unnecessary drug side-effects, and death in some of the worst cases (6-13). The indirect effects of drug falsification include a loss in government tax revenue and the funding of illegal activity which may include terrorist organisations (14). High profile cases of falsified medicines include anti-cancer agents such as Avastin® (Bevacizumab) (US)(7) and Herceptin® (Trastuzumab)

(UK, Finland and Germany) (9). Epidemic cases of substandard medicines exist, such as those seen in India and Bangladesh, where unsafe levels of ethylene glycol were found in paracetamol elixir. The India and Bangladesh example was responsible for the renal failure and death of over 88 patients (mostly children) (11) and represented an international medicines safety issue.

The prevalence of medicine falsification is difficult to accurately estimate due to its clandestine nature. The World Health Organisation (WHO) estimates that up to 1% of medicines in HIC's (This estimate is not based on data gathered) and 10.5% (95% CI 9.9-11) of medicines in low income and 10.6% (95 CI 10.3-10.9) in middle income countries are counterfeit or falsified (15). This number is estimated to be 50% (estimate not based on data) when considering medicines purchased online (16). The problem of medicine falsification does not only involve tablet formulations but covers the entire formulation spectrum from injectable to inhaled medicines (**Figure 1.0**). Many falsified medicines may contain incorrect or low-grade ingredients, incorrect doses, or may be inappropriately labelled which can result in adverse events, sub-therapeutic treatment or no treatment at all. One of the most serious outcomes from the emergence of medicine falsification is the issue of antimicrobial resistance. Antimicrobial resistance is reaching a global pandemic level and is one of the biggest threats to global health today (17). Since the golden age of antibiotics in the (1970's) there have been few new antibiotic agents discovered, and now due to the global health issue of antimicrobial resistance, existing antibiotics are under threat.

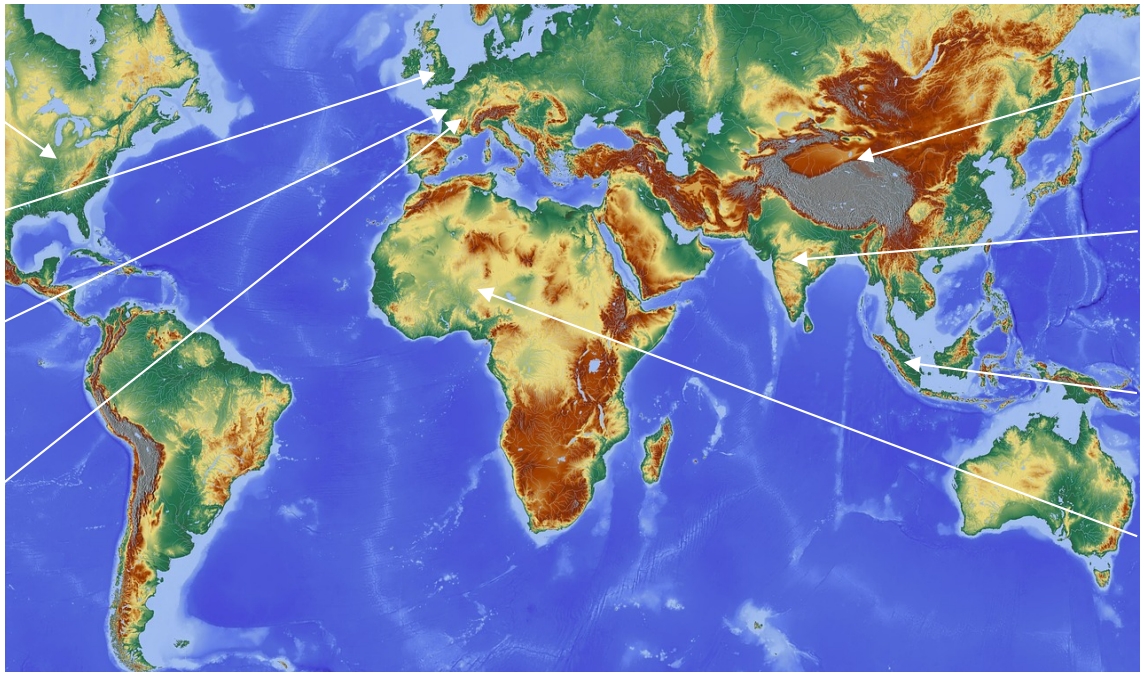
Resistance is caused by inappropriate use and irrational prescribing of legitimate medicines but may also be adversely affected by falsified and substandard medicine use. Patients may purchase substandard and falsified medicines either unknowingly or without comprehension of the issues associated with taking poor quality medicines. These substandard medicines may be fake medicines purchased online, from street vendors, unknowingly supplied by healthcare facilities, or may be medicines which are legitimate and not appropriately stored in countries with high average temperatures and low levels of health literacy or understanding of adequate drug storage.

Avastin 400mg/16ml infusion. Cancer. USA. 2012. £924.Contained no active ingredient [A]

Seretide 25/250mcg evohaler. Asthma. UK. 2009. £59. Recalled product. Harm is un-quantified [B]

Aspirin 75mg tablet. Antiplatelet. France. 2013. 81p (1.2million doses). Contained glucose only [C]

Herceptin 150mg infusion. Cancer. Austria, Finland, Germany, Sweden, UK. 2014. £407. Diluted product or containing the antibiotic ceftriaxone [D]



Glibenclamide tablet. Diabetes. China. 2009. £8. Contained 6 times the normal dose. [E]

Paracetamol Syrup. Bangladesh and India. 1990 onwards. £3. Syrup contained the toxin diethyl glycol. Killing at least 88 people in India and Bangladesh. [F, G]

Erectile dysfunction drug. Singapore. 2008. Contained glyburide, an antidiabetic drug. 150 hospitalised, 7 with severe brain injury. Four died [H]

Antimalarial. 39 countries, Sub-Saharan Africa. Substandard products resulting in treatment failure and ~122,350 deaths in children under 5 years of age [I]

Figure 1.0: A selection of falsified and substandard medicine incidents worldwide (* pricing for an original pack, according to British National Formulary, February 2018).

A.www.fda.gov/Drugs/DrugSafety/ucm291960.htm
B. www.gov.uk/drug-safety-update/counterfeit-medicines-what-pharmacists-should-know
C. www.safemedicines.org/2013/05/french-customs-seizes-12-million-doses-of-counterfeit-aspirin.html
D. www.medicinesauthority.gov.mt/file.aspx?f=903
E. The Effects of Falsified and Substandard Drugs.Countering the Problem of Falsified and Substandard Drugs.NCBI Bookshelf [Internet]. [Cited 2016 Feb 17]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK202526/#ref_000225
F. Hanif M, Mobarak MR, Ronan A, Rahman D, Donovan JJ, Bennish ML. Fatal renal failure caused by diethylene glycol in paracetamol elixir: the Bangladesh epidemic. BMJ. 1995 Jul 8;311(6997):88–91.
G. Singh J, Dutta AK, Khare S, Dubey NK, Harit AK, Jain NK, et al. Diethylene glycol poisoning in Gurgaon, India, 1998. Bull World Health Organ. 2001; 79(2):88–95.
H. http://www.who.int/bulletin/volumes/88/4/10-020410/en/
I. Renschler JP, Walters KM, Newton PN, Laxminarayan R. Estimated Under-Five Deaths Associated with Poor-Quality Antimalarials in Sub-Saharan Africa. Am J Trop Med Hyg. 2015 Jun 3; 92(Suppl 6):119–26

1.1: Terminology

In recent years, the term counterfeit has been used interchangeably with the term falsified which has confused discussion internationally. To understand these terms relevant government and non-government organisation websites and publications were searched to identify the most common terminologies used by each organisation. The European Medicines Agency (EMA), the US Food and Drug Administration (FDA), the World Health Organisation (WHO), the European Commission (EC), UK Legislation national archives, European legislation publications and websites were searched to identify the terminologies used by each organisation.

The current definition of a falsified medicine as defined by European and UK law is any medicinal product with a false representation of '(a) its identity, including its packaging and labelling, its name or its composition (other than any unintentional quality defect) as regards any of its ingredients including excipients and the strength of those ingredients; (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or (c) its history, including the records and documents relating to the distribution channels used' (18-20). The WHO previously used the all-encompassing term 'Spurious/Falsely-Labelled/Falsified/Counterfeit (SFFC) Medicines'. This term related to medicines which were deliberately and fraudulently mislabelled with respect to identity or source. This term has recently been relinquished and replaced with the terms Substandard and Falsified (SF) and unlicenced or unregistered

(**Table 1.0**). The problem with using the term ‘Counterfeit' and ‘Falsified' interchangeably is that the former refers to intellectual property breaches and the latter refers to medicines that try to pass themselves off as a legitimate product. In Europe, there is a clear line drawn between both ‘falsified' and ‘counterfeit' medicines. The EMA classifies a counterfeit medicine as any medicinal product that does not comply with intellectual property rights or infringes on trademark law (21), and falsified medicines are defined as fake medicines that pass themselves off as real, authorised medicines (22). In the US the term counterfeit is used in all cases. The US legislation does not refer to falsified medicines and instead refers to counterfeit medicines. In the US the term ‘Counterfeit’ used to describe both intellectual property breaches and fake medicine. The FDA describes a ‘Counterfeit' medicine as ‘A fake medicine. It may be contaminated or contain the wrong or no active ingredient. They could have the right active ingredient but at the wrong dose’ (23).

It is essential that the international community recognise the single SF definition described in **Table 1.0**, not only to harmonise discussion internationally but to standardise the legal penalties for the manufacture and distribution of SF and counterfeit medicines. As a result of the new WHO definition, most countries use the term SF medicine however due to use of the term counterfeit in US legislation; ‘counterfeit’ is the preferred term in North America. For this thesis, the Falsified Medicines Directive (FMD) definition of a falsified medicine is used when referring to a falsified medicine. When the term counterfeit is used, this is referring to cases of falsified medicines within the US.

The term 'Fake' medicine is also useful way of describing falsified medicine to the general public. However, the WHO definitions of Substandard and Falsified should be used when discussing this matter on a professional and legal basis. Counterfeit should only be used in the EU when referring to intellectual property infringements.

Table 1.0: A description of medicine quality terms (24).

Term	Definition	Source
Substandard	Also called 'out of specification', these are authorised medical products that fail to meet either their quality standards or specifications or both.	WHO (25)
Falsified	Medical products that deliberately or fraudulently misrepresent their identity, composition or source.	WHO (25)
Falsified	Any medicinal product with a false representation of '(a) its identity, including its packaging and labelling, its name or its composition (other than any unintentional quality defect) as regards any of its ingredients including excipients and the strength of those ingredients; (b) its source, including its manufacturer, its country of manufacturing, its country of origin or its marketing authorisation holder; or (c) its history, including the records and documents relating to the distribution channels used'.	FMD (19)
Unlicenced or Unregistered	Medical products that have not undergone evaluation or approval by the National or Regional Regulatory Authority (NRRA) for the market in which they are marketed/distributed or used, subject to permitted conditions under national or regional regulation and legislation.	WHO (25)
Counterfeit	Any medicinal product that does not comply with intellectual property rights and/or infringes trademark law.	EMA (22)

Counterfeit	A fake medicine. It may be contaminated or contain the wrong or no active ingredient. They could have the right active ingredient but at the wrong dose'.	FDA (23)

1.2: Anti-Counterfeiting and Falsification Laws and Regulations

A literature review of PubMed, Google Scholar, and government legislation archives was conducted using search terms such as 'Falsified', 'Counterfeit', 'Medicine' 'Drug' and 'Regulation', 'Policy', 'Legislation'. Regulations and legislation were identified and summarised in (**Table 1.1.** and **Table 1.2.**). Legislation in Europe and the US relating to medicines falsification, counterfeiting and tracking have been in place for many years. This legislation has been modernised and replaced across Europe, the US, and the rest of the world, most notably the EU Falsified Medicines Directive published in 2011 and the US Drug Supply Chain Security Act (DSCSA) published in 2013.

1.2.1: European Regulation

Table 1.1: European anti-falsification regulations.

The 'Bollini Law' 2001	This change of regulation requires medicines to be tracked to the point of sale using two barcodes, placed on the product at manufacture using an adhesive label in Italy.
Foreign Trade Policy 2015 (26)	General of foreign trade (DGFT) for pharmaceutical products exported from India requires serialisation of medicine from India with a 2D data-matrix barcode before entry into the European market. Examples of which are seen on products in the United Kingdom imported from India. The serialisation of products imported from India employ the GS1 standard serialisation format which comply with FMD standards. These product lines are likely to remain serialised by these standards.

The FMD, introduced in 2011 (18-19) by the European Commission, aims to harmonise legislation and practice across Europe. The main points of the FMD, which are relevant to this thesis are listed below (27).

- A 2D barcode containing a unique product identifier serial number, batch number, expiry date, and General Trade Item Number (GTIN) are printed onto each medicine carton along with the same human-readable data.
- Tamper-evident seals will be required for all serialised products.
- Over the counter medicines (unless deemed vulnerable) will not require authentication.
- All prescription only medicines (unless excluded via risk assessment) will require authentication.
- Before supply to the public, all European pharmacies must decommission medicines.
- Manufacturers are responsible for the cost of the national medicines verification database which facilitates the cross-checking of 2D barcodes against a known list of legitimate products.

It is likely however that changes to pharmacy workflow and costs generated within the pharmacy itself, as a result of the FMD, will not be the responsibility of the manufacturers. These costs will be the responsibility of community pharmacies, GP practices, hospitals and any other groups that are governed by FMD regulations and are involved in medicine dispensing.

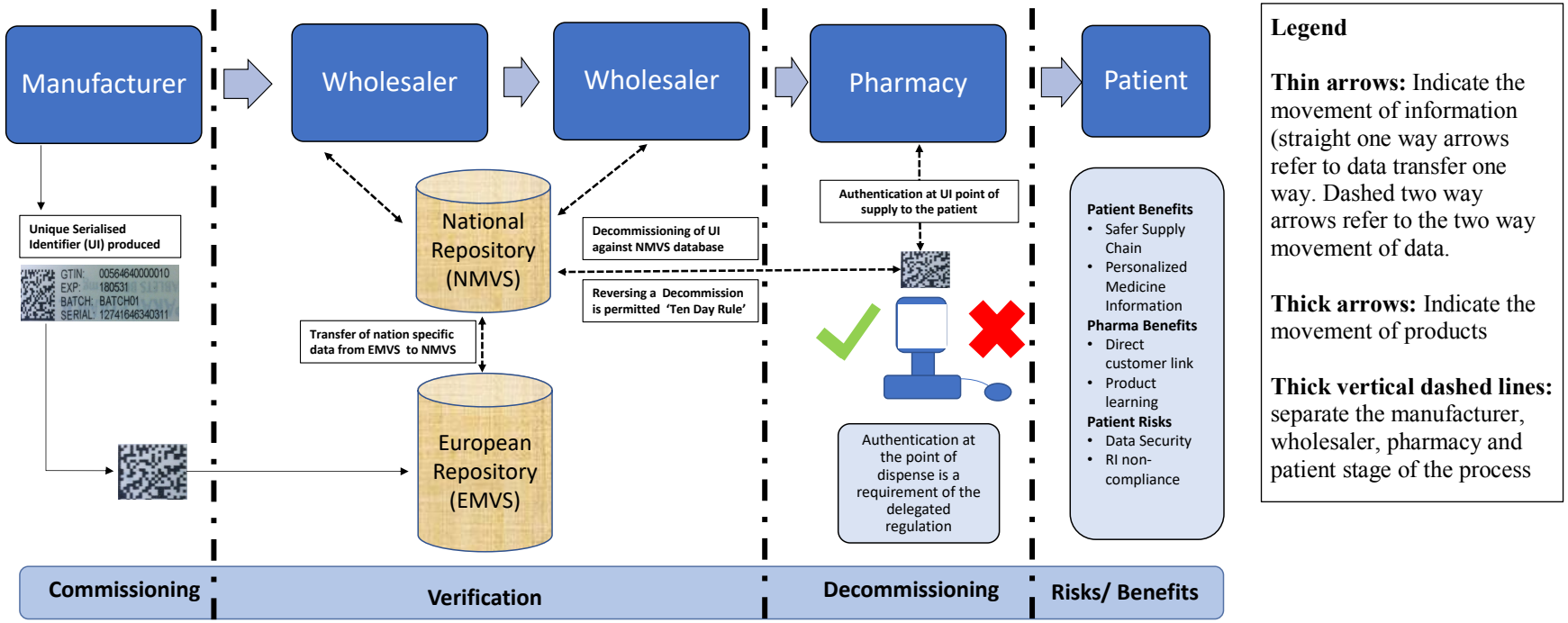
At manufacture product data regarding the batch number, expiry date, unique identifier, GTIN, reimbursement code (if adopted by member states) contained within the 2D data matrix is attached to each product package. This data, along with the anticipated country of issue or sale will be directed to the European Medicines Verification System (EMVS) this is illustrated in **Figure 1.1**. This information is then sent to the relevant

national medicines verification system (NMVS); dependant on the intended country of sale **(Figure 1.1**). Medicines are then scanned by the pharmacist upon supply to the patient to ensure the medicine has not been falsified, recalled or reached its expiry; with certain dispensations for the secondary care setting The FMD also covers important issues such as medicines sold online and introduces a pan-European EU common logo to identify legitimate medicine suppliers. There is no reference within the FMD legislation which relates to patient verification.

The delegated regulations, which followed the FMD, published on February 9th, 2016 are a series of instructions further describing the FMD product safety features. These regulations detail the requirements for manufacturers, wholesalers and pharmacies (both primary and secondary care) and mark a three-year countdown to compliance across all affected sectors of healthcare (February 9th, 2019). Chapter two builds on the information from chapter one and takes a deeper look in to the FMD and how it relates to the hospital pharmacy sector.

UK and Brexit

The UK is due to leave the EU on 29th March 2019. The FMD scanning of 2D data matrices by dispensers is due for full implementation by February 9th 2019. The FMD has already been added to UK law. It could be removed post Brexit however there has been no indication from the MHRA that this will happen.



Legend

Thin arrows: Indicate the movement of information (straight one way arrows refer to data transfer one way. Dashed two way arrows refer to the two way movement of data.

Thick arrows: Indicate the movement of products

Thick vertical dashed lines: separate the manufacturer, wholesaler, pharmacy and patient stage of the process

Figure 1.1: Post FMD product and data movement through the pharmaceutical supply chain.

1.2.2: US Regulations

A number of regulations existed prior to the most recent legislation; the Drug Supply Chain and Security Act. These regulations are listed and explained in **Table 1.2**.

Table 1.2: US anti-counterfeiting legislation before 2013.

The US trademark act 1946 (Also known as 'The Lanham act') (28)	States that anyone who shall without the consent of the registrant, counterfeit during production, be liable for civil action and further describes the penalties for reproducing or counterfeiting without permission.
Trademark counterfeiting act of 1984 (29)	Amends the US trademark act 1946 and has made the use of a counterfeit trademark an offence.
Food, drug, cosmetic, and device safety amendments of 1992 (30)	Includes amendments that direct the secretary of health and human services to cease production and recall any issued food, drug or cosmetic if it has a probability of causing health consequences or death.
The anti-counterfeiting consumer protection act of 1996 (31)	Amends the US trademark act 1946 allowing the court to seize vehicles used for transporting counterfeit goods and also awards statutory damages to plaintiffs instead of actual damages or profits. This act also amends the tariff act of 1930 and importantly permits the secretary of the treasury to destroy forfeited counterfeit trademark products. This act also details civil penalties for 'aiding and abetting' the importation and sale of products with a counterfeit American trademark. Section 10 states that limits on fines are set based on first and second seizures, but more importantly, these fines are 'based on the value that the merchandise would have had if it were genuine' and not based on their market value as counterfeit products, which is a greater penalty to counterfeiting criminals.
Anti-cybersquatting consumer protection act of 1999 (32)	Signed by President Clinton in 1999, this is an act in US history which relates to the sale of goods via websites that deceive affiliation. This act protects patients from purchasing counterfeit medicines from sources perceived to be reputable.

Counterfeiting of manufactured goods act 2006 (33)	Before this act, signed by President Bush in March 2006, only counterfeit goods could be confiscated. This act rectified this anomaly and now permits the confiscation of the equipment used to produce and package counterfeit goods also, with a further provision to prohibit trafficking in counterfeit labels, stickers, and other markings. The fine structure also sees change for counterfeiting criminals, introducing fines as high as 15 million.
Counterfeit drug penalty enhancement Act of 2012 (34)	This bill, which aims to increase penalties and prison sentences for traffickers of counterfeit products, increases the penalty for those who counterfeit medicines and requires the attorney general to give increased priority to cases relating to counterfeit drugs. This legislation was required following the importation and distribution of a counterfeit Roche product (Avastin®) to a number of US doctors in February 2012. This counterfeit drug contained chemicals ranging from starch to salt with some cases containing solvents such as acetone and caused widespread concern throughout the legal drug supply chain. Considering there were 385 federal prosecutions for counterfeiting goods between 2006 and 2010, the mean sentence was only 10 months; a penalty that does not reflect the crime committed. The counterfeit drug penalty enhancement act increased the penalty which now includes a fine, imprisonment for any term of years including life, or both, for trafficking in counterfeit drugs.

The US Drug Supply Chain Security Act (DSCSA) 2013 which is title II of the US Drug Quality and Security Act, pertains to the regulation of the drug supply chain and increases security via the tracing of prescription-only medicines and their associated records electronically from the point of manufacture to the pharmacy (35-36). This act, similar in many ways to the European FMD, requires manufacturers to attach or imprint a unique product identifier onto each medicine container. The act requires that all previous transaction data is provided at the point of transfer from one verified party to another **(Table 1.3).** Similar to the FMD, packages returned to manufacturers, wholesalers or re-packagers

for resale shall be verified before future distribution. This act has the potential to generate enormous change within the US healthcare system, promoting supply chain security and helping to prevent the occurrence of future counterfeiting cases. The final compliance deadline for dispensers is 2023 with further deadlines in place for other stakeholders (35).

Table 1.3: Transaction terms and definitions (35).

Term	Definition
Transaction History (TH)	A statement in paper or electronic form with the transaction information for each prior transaction going back to the product manufacturer.
Transaction Information (TI)	Information including the product's proprietary or established name, strength and dosage form, product NDC number, container size, number of containers, product lot number, transaction date, date of the shipment (if more than 24 hours after the transaction) and the entities' business names and addresses transferring and receiving product ownership.
Transaction Statement (TS)	Substantiation in paper or electronic form that the entity transferring ownership is authorised to receive the product.

Mutual and Specific Requirements for Supply Chain Partners

The DSCSA describes some stakeholder requirements, some apply to all parties (mutual), and some contain subtle differences between the supply chain actors (exclusive). The DSCSA impacts all partners regarding trading, quarantine, returns practice, medicine verification, responding to alerts and the opportunity to use an external electronic database provider.

Mutual Requirements

(A) Trading

From 2015, all stakeholders shall trade only with authorised trading partners. The transaction data (**Table 1.3**) is to be exchanged at each transaction and data relating to each transfer of ownership shall be maintained for not less than six years. In the event of a recall or for investigations, the manufacturer's wholesalers and repackagers shall provide the transaction history, transaction information and a transaction statement for the relevant product no later than one business day or 48 hours after receiving the request, whichever is the shortest time. In the case of dispensers, the dispenser shall provide appropriate information no later than two business days after receiving the request (or another reasonable time as determined by the secretary).

(B) Quarantine

By January 2015 all relevant stakeholders shall have systems in place to deal with suspect product quarantine, product investigation and cleared products (when a suspect product is found to be legitimate) and keep records of investigations of suspect products for not less than six years after the conclusion of the investigation.

(C) Returns

When saleable products are returned, wholesalers and repackagers must provide transaction data, and the verification of medicines shall

occur. However, dispensers are not required to provide such data when returning products. Regarding non-saleable returns, transaction data (**Table 1.3**) does not need to be provided by any stakeholder.

(D) Electronic Database

A pharmaceutical company, wholesaler, repackager or dispenser may satisfy the requirement of the DSCSA by operating a database under their control or by utilising a secure database operated by another entity. The entity providing this database shall provide the requirements set out by this act and respond to requests; they may also provide data to other members of the pharmaceutical distribution supply chain. The use of an external entity to provide this database does not exempt the manufacturer from requests to verify medicines.

Manufacturers' Specific Requirements

From November 2017, manufacturers shall affix or imprint a product identifier to each package or the homogeneous case of a product intended to be involved in a commercial transaction, and manufacturers should maintain the product identifier information for not less than six years.

(A) Suspect and illegitimate products

In addition to the systems and processes required for suspect products mentioned previously, manufacturers must have further systems or processes in place for product disposition within the organisation as well as aiding in trading partner disposition of the affected product. In the case of illegitimate products, a manufacturer is to retain a product sample for further investigations and prepare for making notifications, responding to

notifications, terminating notifications and retaining records of notifications for not less than six years after the conclusion of the disposition.

(B) Requests for verification

From November 2017, manufacturers are to accept requests for product verifications from an authorised repackager, wholesaler or dispenser and reply within 24 hours to notify the interested party as to the status of the queried drug i.e. whether the product identifier, including a standardized numerical identifier (SNI) on the product, matches the manufacturer's records. If there is a disparity between the products SNI and the manufacturer's records this product shall be treated as suspect, therefore triggering an investigation.

Wholesale Distributor Specific Requirements

When dealing with returns, wholesale distributors may accept returns from dispensers and repackagers only if the returned product can be associated with the relevant transaction information and transaction statement. If a wholesaler wishes to make a non-saleable return of a product to a manufacturer then in general terms transaction statements and associated information is not required. Starting from November 2019, wholesalers may only deal with products which are encoded with a product identifier (some exceptions may apply), distributors may disclose transaction information, e.g. transaction history and lot level information

in the presence of a written agreement between the wholesaler and the purchaser.

(A) Suspect and Illegitimate Products

If a wholesaler understands that they are in possession or control of a suspect product or have been made aware by the secretary the following steps are to be taken:

1. Quarantine such a product until it is cleared or dispositioned.
2. Notify the Secretary.
3. Conduct an investigation in association with trading partners within the supply chain.

TH's and TI's shall be validated and starting November 2019 the product shall be verified at package level including the standardised numerical identifier. If such a product is subsequently cleared, a notification shall be made to the secretary, with the wholesalers retaining investigation records for not less than six years. Should a suspect product be found to be an illegitimate product, the wholesaler shall quarantine the product until disposition and take reasonable action to facilitate the disposition of products in the possession of trading partners. Samples of illegitimate products should also be kept for laboratory analysis.

Dispenser Specific Requirements

The dispenser shall supply the same information as manufacturers, wholesalers and repackagers when transferring ownership of a product to another owner with the exception of (i) supply to another dispenser to supply a specific patient need and (ii) dispensing to a patient. The dispenser shall also capture the TI, TH and TS as part of a suspect or illegitimate investigation and maintain such information for not less than

six years following the transaction, although a dispenser may enter into a written agreement with a third party to confidentially maintain such data.

Dispensers are to have systems in place to comply with the DSCSA's requirements in identifying 'suspect' and 'illegitimate' products under product verification processes. When a product is determined to be suspect, the dispenser shall quarantine the product and 'promptly' investigate to determine if the product is illegitimate. If a product is determined to be illegitimate, within 24 hours of making this determination, the dispenser must notify the FDA and all relevant trading partners.

Unlike other trading partners, who must investigate all suspect products, dispensers are only required to verify the product identifier of at least three packages or 10% of such suspect products, whichever is greater. Similarly, until November 2017, there is a significant exception from the requirement for pharmacy dispensers to respond to requests for information from FDA or state officials. In the event of a recall, dispensers may be asked for information by government officials only if such recall involves a serious adverse health consequence or death to humans.

From November 2020, a dispenser will engage in transactions only if a product is encoded with a standardized numerical identifier (SNI) that includes, in both human-readable forms and on a machine-readable data carrier, the product's lot number and expiration date. Serialisation is achieved through the use of product identifiers (SNIs) within phase I of DSCSA implementation.

Repackager Specific Requirements

From November 2018, a repackager shall affix or imprint a product identifier to each package and homogenous case due for the transaction, maintain this information for six years after the aforementioned transaction and engage in transactions encoded with a product identifier (some exceptions exist). As with manufacturers, wholesalers and dispenser, suspect medicines should be quarantined until proven to be illegitimate or cleared. Any products found to be illegitimate shall be notified to the secretary within 24 hours and dispositioned with a sample of the product retained for analysis. During the investigation process, the repackager shall co-operate with the relevant supply chain partners associated with the product in question and any records relating to an investigation shall be retained and maintained for not less than six years.

Political Changes

In 2017 Mr Donald Trump was elected president of the United States, although Mr Trump has expressed distaste towards the over-regulation imposed by the FDA, so far this largely relates to the licensing of new medicinal products (37). Regarding anti-counterfeiting and tackling IP infringements Mr Trump has published an executive order which announces that secretary of homeland security shall develop a plan to combat violations of US customs laws, the enforcement of laws to 'protect intellectual property right holders from the importation of counterfeit goods'(38). Although this executive order supports the idea of protecting IP owners from counterfeiting, it is still unknown, whether or not President Trump will make changes to the DSCSA described above.

1.2.3: Rest of the World Regulations (non-exhaustive list)

The FMD and DSCSA are recent, high-profile examples of regulations relating to medicine falsification and counterfeiting. These regulations are due for complete implementation by 2019 and 2023 respectively; however, many international regulations previously existed. Countries such as India, Argentina, Brazil, South Korea, Turkey and China all have regulations in place, and many other countries are drafting regulations or continuing with medicines serialisation in the absence of regulations.

India

India has implemented a track and trace system and central data portal for exported medicines according to the Directorate General of Foreign Trade. This policy change takes into consideration primary, secondary, tertiary medicine packaging and requires data relating to packaging to be uploaded to the central portal of the government of India or a designated agency before releasing drug formulations for sale or distribution (26).

Primary packaging

Although India plans to place a 2D barcode on the primary packaging of drug formulations (the packing in direct contact with the active ingredient) with human-readable data, this currently is optional and has been placed on hold (26).

Secondary Packaging

India has opted to include a one or two-dimensional barcode (1D or 2D) with a 14-digit GTIN along with a batch number, expiry date and

unique serial number on medicines' secondary packaging (e.g., outer carton).

Tertiary Packaging

A 1D code must be placed on tertiary packaging, i.e. serial shipping container code. This change of regulation via public notice was published on 5 January 2016 (26). The requirement for printing barcoding on the packaging is already in place. All manufacturers must maintain and upload the parent-child packaging relationship data onto the central portal, effective from 31st March 2016. An exemption is in place, however, for small-scale industrial (SSI) manufacturers, deferring maintenance of parent-child relationship data on the packaging until 31 March 2017. Even SSI manufacturers are required to upload tertiary-level data onto the central portal from 22 May 2015 (26).

Serialised product records should be maintained by the manufacturer until six months after the product expiry date (39).

Argentina

Argentina has implemented a GS1 standard traceability system with central portal and serialisation through regulation 3683 (39-40). Under this regulation, each medicinal unit will be given a unique identifier that includes a batch number and expiration date. This regulation has taken a different approach to implementation. It does not aim to serialise all prescription medicines from the outset, as the FMD does. Instead, it has started with an initial list of medicines to be included in the serialisation scheme and to add to this list in subsequent years. In 2012, critical-risk medicines such as antibiotics, insulin, clotting factors, a range of

cardiovascular drugs and central nervous system drugs such as those for epilepsy and Parkinson's disease were included. More than 200 drugs were added to the traceability scheme in 2013 (39-40). Pharmaceutical companies are required to store an unambiguous code supervised and audited by the National Administration of Drugs, Foods and Medical Devices (ANMAT) on each unit pack, and all information must be provided in Spanish, with all codes complying with GS1(Global Standard One) format. Each supplier should place a unique identifier, batch number and expiration date on each unit, i.e., a GS1 standard 2D data-matrix. Each supply chain actor must record 'logistical movements' of drugs and supply that information to the ANMAT-managed database in real-time.

Brazil

Brazil has introduced a regulation mandating the serialisation of medicinal products. Brazilian federal law 11.903 of 2009 (41) requires 2D serialisation (with human-readable text) of secondary packaging with data relating to tracking medicines requiring transmission to the Brazilian Health Regulatory Agency (ANVISA). Packaging serialisation will be accompanied by a tamper-evident stamp, and supply chain protagonists will be required to transmit data to ANVISA. A 180-day implementation timeline for manufacturers and a one-year period for the other supply chain members start upon publication of the final regulation (39). Brazil required all manufacturers to serialize and trace three batches of products through the supply chain before 10 December 2015 and unit level serialization and tracking on all medicinal products by 2016 (42).

South Korea

South Korea has issued a Ministry of Health and Welfare Notification 2011-58. This notification requires a barcode or radio frequency identification (RFID) tag to be applied to primary, secondary and external containers and medicines' packaging materials manufactured within or outside South Korea. Expiry date and lot number are required for traceability of a selection of drugs from 2012 and prescription-only drugs from 2013.

Turkey

Turkey was one of the first countries to implement unit level serialisation and a centralized government portal. One of the key reasons for implementing medicine serialization in Turkey was to reduce reimbursement fraud. Pharmacists were required to scan a 2D data matrix barcode before reimbursement. The Turkish system has evolved to require medicines to be scanned at multiple stages before the pharmacist supplying the product to a member of the public. The identifiers included in the Turkish 2D data-matrix include a global trade item number (GTIN), serial number, expiration date, batch/lot number and group separator with accompanying human-readable data.(43- 44) Data-matrices were added to products after the publication of Regulation no. 26775. Sale of medicines produced before this date was permitted until 31 December 2009 (43- 44).

China

The China Food and Drug Administration (CFDA) enforced the serialisation of individual saleable pharmaceutical products (unit level) and case level with a 20-digit code, a central portal (China drug

identification, authentication and tracking system) was also implemented. Full serialization of all medicinal products was due by 2015 and, although pharmaceutical companies continue to serialise products, at this stage the current traceability system has been placed on hold (43, 45) CFDA also has encouraged the National Institute for the Control of Pharmaceutical and Biological Products (NICPBP) to extend drug surveillance among rural areas by using mobile laboratories, disguised as vehicles (white vans), that are equipped with instruments and chemical analysis technologies, including Wi-Fi-connected computers and near-infrared spectrometers.

1.3: Methods to Detect Falsified Medicines

A literature review covering the methods to detect falsified medicines was conducted. This review searched Science Direct, PubMed, Google Scholar and grey literature using the search terms 'Detection', 'Identification', 'Analysis', 'Screening', 'Falsified', 'Counterfeit', 'Medicine', 'Drugs' and 'Technology'. This search found research papers which identified a number of different approaches used to detect falsified medicines and in some cases the effectiveness of the approaches (**Table 1.4)**. The mode of action of each technology is explained with basis advantages and disadvantages also described.

From the literature review, it is evident that the detection of falsified medicines is a practice usually conducted by field researchers (from universities and non-government organisations) and customs officers at international borders or as part of internet pharmacy investigations. There are some exceptions, such as Belgium, Italy and Greece where individual medicines are serialised and digitally verified against a list of products known to be legitimate. There are many methods at the disposal of investigators which include traditional laboratory techniques, less frequently used emerging technologies and visual checklists (**Table 1.4**), with advertising and awareness campaigns (**Table 1.5**) also playing an important role in educating patients and healthcare professionals to the threats of counterfeit medicines.

For the moment, it appears that cross-border checks are responsible for many counterfeit or falsified drug seizures worldwide;

however, it would appear that random customs checks alone are no longer suitable in the face of a growing international drug falsification. As a result of random searches or notifications through international criminal communications, customs officers identify and investigate suspicious packages of medicines crossing international borders with samples traditionally sent to laboratories for analysis using methods such as chromatography or spectroscopy. This practice alone is proving ineffective, as counterfeit medicine rates increase year on year (46). Cross border checking, for example, do not account for counterfeit/falsified medicines made in the same country that they are sold or supplied.

Random custom checks are important, but systematic medicines verification checks are also useful. Criminals work in a clandestine manner, making every effort to bypass safety and security systems put in place to protect patients; therefore, an evolving multi-prong, multi-stage approach to counterfeit or falsified medicine detection is required. With the advent of relatively inexpensive, emerging portable methods to identify counterfeit drugs, the future could see checks carried out not only by customs officers and field operators but also doctors, pharmacists upon supply to a patient, nurses upon administration to a patient or even by the patient themselves.

It is important to understand the methods and technologies available to detect falsified medicines and to comprehend their advantages and disadvantages in light of a multi-prong, multi-stage approach to SF medicine detection.

Table 1.4: A summary of available methods to detect substandard and falsified medicines.

Laboratory		
1	**Chromatography**	LCMS(47), LC-QTOF-MS(48), TLC(49), HPLC (48).
2	**Spectroscopy**	FTI(49), MIR(50), NIR(48)(51-52), NMR(50)(52) Raman (51) and XRF(48).
3	**Other Analytical Methods**	X-Ray Diffraction (52), Chemical-Physical Tests (colorimetric (52-53), dissolution (54), density and viscosity(55), Dynamic Thermal Analysis (54), Micro Fluidics (56) and UV (57-59).
Emerging technologies		
1	**Handheld Devices**	CD3 (60-61), TruScan™ (51-52, 62), Scio. (63).
2	**Mini-laboratories**	King QRS (64), GPHF minilab (65, 62), Pharma check (59, 66).
3	**Mobile Phone or Social Network**	MPedigree (66-69), Sproxil, Authenticait, Pharmasecure, Epothecary and Medscape (70).
4	**Serialization and Verification**	RFID(71,72), 2D Serialization (73).
5	**Edible Serialized Trackers**	TrueTag (62), Nanoguardian (62).
6	**Algorithms and Data Security**	Machine learning for increasing the identification of illegal online pharmacies, blockchain for securing data during the authentication of medicines (70).

Visual checking	
1	The WHO Checklist (50,64).

1.3.1: Laboratory

Many laboratory techniques used for the detection of counterfeit drugs are the same techniques used in the synthesis and analysis of medicinal products for manufacturing or research purposes. Such techniques are usually required for in-depth analysis and provide time-delayed responses to field investigators or customs officials. These approaches include chromatography, spectroscopy and a number of other individual methods which are explained below. The following approaches to SF medicine detection and associated publications identify how these techniques work. Sensitivity or specificity of these techniques were largely unreported in these studies. There was also little or no reference to the cost per test for each technique.

Chromatography

This technique relies on a mobile phase (solvent) and a medium (e.g. chromatography paper) which is used to separate a chemical mixture into its multiple compounds. The compounds are separated at different stages on the chromatography paper, revealing the makeup of the mixture or product. This overarching term covers multiple analytical techniques, including thin layer chromatography (TLC) and high-pressure liquid chromatography (HPLC). These techniques can also be combined with

spectroscopy to analyse compounds, e.g. Liquid chromatography-mass spectrometry (LCMS).

Bernard et al. (47) demonstrates the use of chromatography, namely LCMS, as a technique to identify counterfeit cardiovascular drugs in Africa. This research pilot identifies the technique as a valuable method to identify drugs, however, due to a relatively small sample size, the experiment was not exposed to nor did it detect any falsified medicine, therefore this research is not entirely useful in determining the effectiveness of this technique. Lee et al. (48) demonstrated the role of liquid chromatography quadrupole time-of-flight mass spectrometry (LC–QTOF–MS), where a spectral library of sildenafil and associated analogues were generated to allow for the identification of falsified medicines. Custers et al. (49) describes TLC as slow but easy and cheap. Custers identifies HPLC coupled with ultraviolet detection or mass spectrometry as a more expensive and sophisticated method of identification.

It is clear that chromatography can identify medicines that are entirely different however there is no evidence from this study that chromatography alone could differentiate between chemically similar drugs such as morphine and codeine or counterfeit drugs which contain similar doses of the active ingredient. Moreover, chromatography is a destructive technique which renders the tested product unusable. Furthermore, chromatography is time-consuming, requires the use of a laboratory, a number of materials, and trained lab technicians. The training required and cost of materials makes chromatography an expensive

approach subject to human error and unsuitable for routine verification in isolation, but yet an important tool in a multi-approach to falsified medicine detection.

Spectroscopy

This term categorises some of the techniques identified as possible counterfeit drug detections methods. By definition spectroscopy is '*The branch of science concerned with the investigation and measurement of spectra produced when matter interacts with or emits electromagnetic radiation*'(74). Spectroscopy covers a variety of techniques. Each technique utilizes a different type of radiative energy involved in the analysis interaction. These techniques include Fourier-transform infrared spectroscopy (FTI)(49), mid-infrared spectroscopy (50) (MIR), near-infrared spectroscopy (NIR)(48, 51-52) nuclear magnetic resonance spectroscopy (50-51)(NMR), Raman spectroscopy (51-52), and X-ray fluorescence spectroscopy (XRF)(48).

In the past, the process of preparing a sample for spectroscopy analysis required the crushing of a product with or without further dissolution. This dissolution process required preparation, staff training and time. However refractory spectroscopy using MIS, NIR and Raman spectroscopy can be a relatively quick process involving little or no sample preparation. NIR and Raman spectroscopy analysis can be performed on medicines without destroying the product (52). When compared to chromatography, which requires the separation of products into active ingredients, the spectroscopy approach is preferred due to its potentially non-destructive nature. NMR, on the other hand, does require

the dissolution of a solid sample for testing, (49-50) and the results generated are almost indisputable. If NMR analysis was used it would occur after the medicine is initially identified as suspicious or counterfeit using a cheaper identification technique. The NMR analysis process involves the employment of a large facility rarely found outside of a pharmaceutical company or university chemistry laboratory, making this expensive instrument largely inaccessible for efficient, routine use. However, with the advancement of emerging technologies, spectroscopy instruments are becoming increasingly available in portable variations, encouraging their use as first-line detection methods.

Other Analytical Methods

X-ray diffraction has also been identified as a method to detect falsified medicines. There is an argument proposed by Maurin et al. (75) which favours x-ray diffraction above NIR. This study tests the X-ray diffraction technique and generates drug results for both legitimate and falsified drugs and explains that the comparison between falsified and legitimate samples show a clear distinction. The author explains that the differences seen with NIR are not as clear as X-ray diffraction and as such required detailed analysis to identify differences from legitimate and falsified medicine results.

Chemical-physical tests such as colorimetric tests, (53,76) dissolution tests (54) or density and viscosity tests (55) can be cheap, effective and easy to perform, these tests are, however, generally regarded as less specific (50).

Wilczyński et al. (55) describes the use of dynamic thermal analysis in detecting falsified medicines. This technique involves the heating of a tablet to 60°C and comparing data such as thermographs of known legitimate medicines with those being tested. The process takes into consideration both tablet content and coating, as differences in product coating may affect product cooling. This technique is simple and requires no sample preparation. Although a temperature of 60°C means that further testing of the sample would not be possible. Heating a medicine to such an extent would contradict the manufacturer's storage requirements of almost all medicinal products, rendering the medicine unusable for therapeutic use.

Colorimetric testing using paper microfluidics is typically engaged for the identification of suspicious artesunate, an anti-malarial drug. Koesdjojo et al. (56) have developed a kit containing paper-based test strips that perform the colourimetric assay upon adding an artesunate sample. The test kit utilises paper microfluidics (four layers with dried reagents) and is based on the reaction of an alkali decomposition product of artesunate with a diazonium salt, fast red TR, that results in an appearance of a yellow colour in the presence of artesunate. This test kit allows for quantitative analysis of artesunate tablets by providing a key that comes along with the kit. It is possible to also use a colour analyser on a camera phone to take a digital image of the chip and analyse the colour. The intensity of the yellow colour produced corresponds to the approximate concentration of artesunate. The specificity of colourimetric detection is dependent on pH, and among a list of other anti-malarial

artesunate is the only drug that gives a yellow colour at a pH of 4. Therefore, the reaction must be maintained at pH 4 to be specific to artesunate and avoid positive test results in the presence of certain other antimalarials. This test appears effective as an initial tool, but due to the equipment and process it would require adaption for testing further medicine and as such would not be suitable for rapid systematic detection.

Ultraviolet light is also used in the detection of counterfeit medicines, usually coupled with other techniques in a laboratory setting and is used by some emerging technologies described below (57-59).

1.3.2: Emerging Technologies

Emerging techniques include the creation of new identification and analysis approaches as well as adaptations of established methods to improve ease of use and portability. Such advances include handheld devices which are usually lightweight, easy to use and more accessible than their laboratory counterparts. Portable and semi-portable minilabs also exist which contain all the necessary functions to perform drug analysis coupled with simple functionality, which allows them to be used by non-laboratory trained staff. Other technologies include SMS networks and medicine serialisation coupled with subsequent verification which include RFID, 2D data matrix and edible medicine trackers.

Hand-Held Devices

The CD3 device is a third-generation handheld electronic tool produced by the FDA which uses light –emitting diodes (led), covering the ultraviolet to the infrared spectrum, for visual fluorescent comparison.

This device compares an image of a known legitimate medicinal product or packages with a suspected counterfeit product image; often falsified medicines or their packaging produce different images under light to legitimate medicines. This device can operate via mains power or can be battery operated making it portable. The price is likely to be much cheaper than traditional lab equipment, therefore it has potential for widespread use (60-61). This technique, however, does not provide an absolute answer and requires interpretation which could be considered a matter of opinion. For example, in a study by Ranieri et al. (61), it was noted that personnel using the CD-3 device, on two occasions identified the authentic medicine as falsified i.e. false positive. Although this is a safer outcome than a false negative, this suggests that misinterpretation is possible. The CD3 facilitates the testing of tablets while still within the original packaging, however only if such packaging is translucent in appearance. This device does not facilitate a response quick enough to be suitable for the routine identification of medicines at the point of dispensing but may prove to be useful in tandem with other techniques, in countries where counterfeiters have developed means to bypass the serialisation process or where such legislation is absent (60-61).

Thermo Scientific TruScan™ is another handheld device relying on Raman spectroscopy, (51-52, 62) to examine the composition of any given product including the API, fillers and coatings. The advantages are that testing is quick and can be performed without destruction of the product or packaging. The device size is substantially smaller than the laboratory version, and as such, it can be used to complete reliable and

repeatable authentication on a daily basis without the employment of highly trained staff.

Scio™ is an example of a new, affordable miniature handheld near-infrared spectroscopy tool which can be used by consumers for pharmaceutical analysis (63). This device is coupled with a mobile phone app and works by comparing the spectroscopy graph results with a database of known legitimate product spectral data to understand whether or not the tested product is legitimate or not.

Mini Laboratories

Kings College London has produced a prototype device called a medicines authentication unit using quadrupole resonance spectroscopy (QRS) (77) is capable of detecting not only counterfeit but also substandard and degraded pharmaceutical products. This process is achieved using radiofrequency spectroscopy, a non- invasive and non-destructive technique; a notable advantage over other analytical techniques (77). Other advantages include the portable nature of the device and the clear Yes/No response, which leaves minimal room for misinterpretation. Considering the clear response, portable nature and analytical intelligence, if scaled appropriately the QRS minilab detection technique may be a viable option alone or in tandem with other detection techniques for routine or field-based detection.

GPHF Minilab unlike the Kings College devise has a four-step process which includes prior dissolution and the use of chromatography to produce a result. Knowledge of analytical chemistry is required to

operate this device which is a major stumbling block for quick, systematic checking. Hall et al. (62) state that the total cost per test per dose is $2 which is also relatively expensive compared to international generic drug prices.

Pharmacheck is another example of a minilab and would appear to use colourimetry in the same fashion as described above (58, 77). This device standardises the process which facilitates mobile testing. Although this product appears to have attracted much media attention, there is not much research published which explains how it operates or how reliable it is.

Social Network and Communication

Mpedigree an African social network company established in 2007 by a Ghanaian entrepreneur which sells software to pharmaceutical manufacturers. This software facilitates the printing of a 12-digit code, concealed by a scratch-off panel onto pharmaceutical containers. Once the code is revealed the consumer can send an SMS message, free of charge, which generates an instant reply describing the authenticity of the product. (67-69) This strategy provides a simple solution to a difficult problem and encourages patient involvement in their healthcare. Furthermore, this technique matches the technology landscape of LMIC's, using SMS messaging as opposed to an internet connection; which can be sparse in developing regions such as sub-Saharan Africa. MPedigree certainly has a role to play in SF medicine detection in sub-Saharan Africa today. However, the strategy would not facilitate direct healthcare provider

verification, as to do so would involve tampering with the unsold product (67).

Other mobile phone technologies have since become available which use a variety of methods to identify medicines as either legitimate or not. Using a products 2D or QR code or texting functionality. New mobile phone approaches such as those produced by Sproxil, Authenticateit, Pharmasecure, Epothecary and Medsnap (70) aim to make medication authentication available to patients.

Serialisation

Radio frequency identification (RFID) is a collective term for technology that uses radio waves to track people or products. The system is made up of a microchip and an antenna (RFID tag); the signalling device is called a reader which also has an antenna. The reader emits electromagnetic waves which are picked up by microchip antenna which modifies the message and sends it back to the reader where the data is converted into readable digital data (71-72). RFID systems are not standard and can vary depending on the product they are attached to. Some RFID's contain their own power source and some feed off energy emitted from the signalling device. This system is frequently used for tracking a product or person and as such demonstrates many advantages for use in the drug tracing industry (72).

Medicine serialisation, verification and authentication require multiple stakeholder compliances to succeed. The approach requires the widespread 2D barcode serialisation of medicines by drug manufacturers;

the risk-based scanning (verification) of medicines by wholesalers and the systematic authentication of the 2D data matrix on the medicine packet at a pharmacy. This method has been proposed by both the EU (18-19) and US (36) governments and is set for international implementation in other nations also. Once implemented is expected to be a cheap and robust way to authenticate the majority of medicines before administration to a patient. This type of tracking also facilitates the identification of expired and recalled medicines (18-19) which may result in some financial advantages for healthcare facilities including better stock control, better waste management, more efficient drug recalls and a change in the reimbursement process, and thereby reducing fraud.

The advantages are not just limited to cost saving but may also relate to improving clinical outcomes. The serialisation method could link patient records to product scanning which would allow researchers and clinicians to identify and compare patient medicine compliance in hospital with compliance in the community. The system could also be used to monitor antibiotic supply to reduce inappropriate antibiotic use. Finally, serialisation could facilitate patient adherence modules with the ability to deliver patient advice at the point of authentication.

Despite these advantages, there are sure to be many workflow adjustments required by manufacturers, wholesalers and pharmacies to comply with impending regulations; which if not handled effectively may cause unwarranted disruption to drug supply in the respective sector. The hospital environment is likely to experience a disruption in the early stages of implementation as this new approach may further complicate an already

complex drug supply process, especially regarding split pack and robotic dispensing, satellite pharmacy hub supply, medicine returns and information technology integration issues between dispensing systems and national databases.

There are many organisations which provide manufacturers with serialisation solutions. These companies can generate 2D barcodes and aggregate codes which is an efficient capability for multipack scanning. There are two companies available to provide a verification system in Europe. Both NMVS providers have been selected by the EMVO and are blueprint providers (78). These companies will be using information technology to check a product code against a national medicine's verification repository and decommission medicines based on the unique codes printed on their carton.

Edible Trackers

Truetag (62) is a low cost edible, heat resistant, tracking micro-tag device manufactured from high purity silica available not only to prevent falsification but also to provide informatics and ensure product quality. Hall et al. (62) explain that an individual pill can be tagged at the cost of $0.01 each and markets it as a technology that is complementary to RFID or 2D barcode authentication.

NanoGuardian (62) also provides individual unit tracing and authentication and can store unique codes. It is compatible with 2D serialisation and RFID tracking. Information stored can include expiry dates and manufacturer information including the drugs anticipated

destination. The positives of these technologies are low cost, high tech., with edible codes available in invisible ink. Regarding systematic authentication, the negatives of this technique, in isolation, are the disruption of individual packs; therefore, these technologies would be best placed in partnership with RFID or 2D serialisation as mentioned previously.

Algorithms and Data Security

Research into machine learning suggests that algorithms can be used to identify and help to close down online pharmacies operating illegally. There are many illegal online pharmacies, and digital approaches could facilitate the identification of these pharmacies in a more effective manner than random identification. Regarding securing the data transmitted during medicine authentication (e.g. as part of the FMD or DSCSA) blockchain technology has been suggested. This approach which has been available for many years, widely associated with bitcoin transactions, can encrypt data every time a pharmaceutical product transfers ownership and acts as a ledger for transactions. Blockchain technology may help to secure this data and reduce instances of unique serial code breaches.

1.3.3: Visual Check

Healthcare professionals are responsible for the systematic checking of medicines to ensure that they are safe for administration. This task falls to pharmacists, nurses and to a lesser extent doctors, due to their limited role in medication dispensing and administration. The general

checking procedure includes an inspection to ensure that the correct product, form and strength have been selected and are in-date. The ability to identify one drug as falsified and another as safe using a standard visual check, where holograms and logos are assessed (52) is based on staff perception. The unstructured approach in a busy environment leaves this process open to error. The 'WHO Checklist' (64) (79) currently available online, adds rigour to the checking processes, introducing a stepwise approach to identifying signs of product falsification. Although this checklist would add significant time to the checking process, until handheld devices such as the CD3 are widely available or until medicine serialisation and verification according to the FMD and DSCSA are fully rolled out; this checklist is the only reasonably resource available for the identification of falsified medicines by healthcare professions. Nursing and pharmacy staff are unlikely to perform the box-ticking exercise associated with the tool exactly. However, education and training surrounding the WHO checklist is likely to increase the chance of detecting a falsified medicine and will also help to raise awareness.

1.3.4: Raising Awareness

Patients are an important group in the fight against falsified medicines, and it is crucial that they are made aware of the signs of drug falsification. Those in LMIC's are especially vulnerable, however, with low levels of education, the ability of LMIC citizens to understand and change behaviours as a result of awareness campaigns remains a problem. Organizations that run awareness campaigns include the WHO, The

Centre for Safe Internet Pharmacies (CSIP), Interpol and The National Agency for Food and Drug Administration and Control (NAFDAC).

The International Medicines Products Anti-Counterfeiting Taskforce (IMPACT) is a WHO group (80) which works on behalf of the 194 (81) WHO member states to tackle the international issues of counterfeit medicines. The group aims to build networks across member states to halt the production of illegal counterfeit medicines. IMPACT have also generated a number of publications pertaining to education and raising awareness. These publications include, 'The impact handbook' (80), 'The BE AWARE toolkit for healthcare professionals' (79) and the 'Counterfeit drugs kill campaign'(82) which details the emotive image of a snake wrapped around medication accompanied by the headline 'Counterfeit Drugs Kill'.

CSIP is a not for profit organisation comprising of internet industry leaders. This organisation aims to alleviate the issues of falsified medicine sales online and have run a number of campaigns. These campaigns include the 'Be safe buy smart' (83) campaign urging patients not to take risks when buying medicines online. The 'Be safe buy smart' campaign has partnered with internet and payment industry leaders such as Google, Yahoo, Microsoft, American Express, PayPal, Visa, and MasterCard to identify and remove thousands of websites delivering counterfeit medicines (83). 'Be safe Rx' is a campaign which is run by the Food and Drug Administration has similar aims to CSIP campaign. Both campaigns raised awareness of the risks associated with buying medicines from illegal online pharmacies (84).

‘Proud to be’(85) is a campaign launched by Interpol**,** the largest international police organisation with 190 members (86). This organisation amongst other activities investigates international crime trends and links national police services together even in situations where previous national relationships have failed. The ‘Proud to be’ campaign focuses on the problem of falsified and counterfeit medicines internationally and features a song which raises awareness by describing the issue through music. In addition to this campaign, operation Pangea (87), a high profile activity, was conducted by Interpol in 2015. This operation continued for one week in June to combat the sale of counterfeit and falsified medicines online, an operation which has grown from 10 countries in 2008 to over 100 in 2015. This operation recovered 20.7 million fakes worth an estimated USD 81 million in 2015 which attracted much publicity. This publicity is likely to deter counterfeiters and raise awareness amongst healthcare professionals and the general public.

NAFDAC in Nigeria often publicise the issue of drug counterfeiting and have been proactive in the identification of counterfeit medicines through the utilisation of emerging technologies such as TruScan™ (handheld Raman spectroscopy), GPHF minilab and mobile authentication services (88).

Table 1.5: A list of organisations and their associated awareness campaigns.

Organisation	Campaign
IMPACT	Counterfeit drugs kill
CISP	Be safe buy smart
FDA	Be safeRX
Interpol	Proud to be
Fight the Fakes	Fight the Fakes
Global Governments	Operation Pangea
NAFDAC	Website advertising: Options available to identify drugs
ASOP	Multiple campaigns against illegal online pharmacies (89)

1.4: Conclusions

The fight against falsified medicines is multifaceted**.** This literature describes the regulations which relate to medicine falsification and counterfeiting and the technological, scientific and practical approaches to identify these medicines. Consumer behaviour requires change, criminal activity in this area requires curbing, effective mechanisms of identification need developing, and policies need to be introduced to tackle this global issue. The ideal anti-counterfeiting or falsification method should be a policy-driven approach which is simple to perform, non-destructive, demonstrates high authentication speed, meets stringent security standards, is cost-effective, and meet the demands of a multitude of stakeholders while integrating coherently with multi-

sector work streams. Unique serialisation appears to be the most appropriate solution however due to poor internet access in LMIC's, serialisation is likely to help HIC's the most initially. Despite the use of serialisation and its growth in recent years, organisations are reminded that falsification or counterfeiting experts will always strive to 'beat the system' which may give rise to the need for multiple or alternative protection measures and frequent campaigns to deter illegal counterfeiters and raise awareness amongst the public.

The argument exists that healthcare professionals and policymakers should understand all tools available in the fight against drug counterfeiting and should not be blind sighted by incumbent legislation, however, the reality of the current legislative situation is that the FMD, DSCSA and other international deadlines are fast approaching. These regulations will play a big role in poor quality medicine detection, and non-compliance with these regulations is not an option.

The medicine screening process using serialised barcodes has worked successfully in Italy, Belgium and Greece for many years in the community pharmacy setting. However, there is little published academic evidence available to support this approach in the primary or secondary care environment. It is useful to conduct a study to understand more about the FMD approach in the hospital environment and to identify the compliance and detection rates of expired, recalled or potentially falsified medicines. It will also be important to identify obstacles to implementation and to identify workflow issues. These are areas which are covered in chapter two.

Note: Large sections of this chapter have already been published in the following article

Naughton et al. 2016. Combating Counterfeit Medicines: Legal Frameworks and Emerging Technologies. RAPS [Internet]. [cited 2016 Jul 18]. Available from: http://www.raps.org/Regulatory-Focus/Features/2016/05/18/24966/Combating-Counterfeit-Medicines-Legal-Frameworks-and-Emerging-Technologies/

2.0: The Impact of The Falsified Medicines Directive on Pharmacy Practice

2.1: Introduction

Chapter one identified and explained a variety of international regulations which relate to medicine falsification and medicine serialisation. Chapter one also identified the technologies available to detect falsified medicines. Considering the international introduction of systematic medicines serialisation and verification, this seems to be the most widespread solution to combat the issue of falsified medicines. It is therefore pertinent to pursue further research in this field. This chapter assesses the FMD, now part of UK law, and its effect on pharmacy practice. This chapter also provides an overview of hospital pharmacy operations and how pharmacies can ensure compliance with the incumbent regulations based on analysis of both community and hospital workflows and the UK drug distribution cycle. This chapter helps to understand potential points to authenticate medicines within pharmacy operations, and also aims to understand some of the advantages and obstacles which are likely to be faced during FMD digital drug screening roll-out (90).

The FMD will bring about positive effects such as increased supply chain security and a reduction in illegal movement of medicines from the intended country of use to another, which causes medicine shortages and price increases. However, less obvious advantages also exist. Once medicines are serialised there will be the potential to better identify short-dated and soon to expire medicines thus reducing

medication waste. There will also be a better understanding and control of stock which will facilitate the cost-effective and efficient recall of drugs when required. If digital medicine screening technologies are integrated into pharmacy medicine record (PMR) software, there will be the capability to deposit individual medicine identifiers into patient records and allow for unprecedented levels of patient-level drug recalls. A better understanding of stock levels will also facilitate a potential reduction in local medicines shortages and a more efficient system of inventory management. As seen in Belgian community pharmacies there will also be the opportunity to load 2D-data matrices with drug specific information relating to adherence, counselling or adverse event recording. Finally, the FMD will generate a wealth of data which will prove valuable for pharmacovigilance purposes and also the monitoring of antimicrobial prescribing and therefore resistance.

The challenges for hospital pharmacy which accompany the FMD relate to the cost of integrating medicines screening or authentication technologies into existing systems. Existing systems include the use of robotics and patient medication records. There will be a cost and inconvenience associated with restructuring pharmacy workflows and added administrative duties which will arise from dealing with the quarantine of recalled, expired and falsified medicines identified by the new technology. The less obvious challenges include the understanding of how the FMD will work in practice and how issues such as how to manage split pack dispensing, pharmacy satellites, aseptic units, ward stock decommissioning, data matrix aggregation, decommissioning unit dose

dispensing, reversing the decommissioning of pharmacy returns and dealing with technological issues such as offline instances.

2.2: Operational Comparison of Hospital Prescription and Dispensing Process Compared to Primary Care

Medicine authentication has existed in the community pharmacy sector, in Belgium, Italy and Greece for over ten years (91). Although there have been pilots in the area of medicines authentication, few appear to have been published, and none appear to have been conducted in a hospital setting (92). There is a difference between hospital and community pharmacy regarding prescription and dispensing workflow processes. These following sections aim to describe the UK community and hospital pharmacy prescription and dispensing workflows to identify obstacles and challenges which may affect the roll-out of medicines authentication technology in both sectors.

2.2.1: UK Community Pharmacy

Within the community sector, the FMD will require the vast majority of prescription-only medicines (POM) and a selection of high risk over the counter (OTC) medicines to be verified for authenticity and decommissioned at the point of supply to the public. The proposed digital authentication technology (software) is likely to be integrated into existing PMR software and will employ the use of existing scanning equipment (depending on the specification of the existing equipment).

Prescription Processing

A prescription may enter a pharmacy in either of two ways. Prescriptions may be sent directly from a prescriber using prescribing software to a designated pharmacy electronically. Alternatively, a prescription may be printed or handwritten by the prescriber and given directly to the patient or representative to fill at a pharmacy of their choice. In the UK printed prescriptions also often have an electronic element; they often have a straight-line barcode which can be scanned in a pharmacy to display the prescription details. For this reason, the majority of pharmacies have barcode scanning equipment.

Electronic Prescription Process

Electronic prescriptions are electronically transmitted daily from GP surgeries to pharmacies. Pharmacies must refresh their e-prescription inbox to identify e-prescriptions. Alternatively, patients may arrive at a pharmacy and indicate to the pharmacist that there is an e-prescription in their inbox (When an e-prescription is identified, a copy is printed by the pharmacist for dispensing. From this point forward, a copy of the e-prescription is treated in the same way as a paper prescription (with the exception of reimbursement).

Paper Prescription Process

A patient may present a paper prescription at a community pharmacy, or they may have their prescription collected from a GP surgery by a member of the community pharmacy team. When a patient arrives with a prescription and delivers it to a counter assistant, the assistant will pass the prescription to a qualified member of staff (dispenser, technician

or pharmacist). The staff member will then generate labels to match the prescription. The staff member will then dispense the prescription by applying the correct label to the correct product according to the prescription. A pharmacist or a technician (usually that has not been involved in the picking, labelling or dispensing of the product) will then check the prescription. If the patient is waiting for the prescription, it is handed directly to them after confirming their identity. If the patient has left the pharmacy, or the patient collects their prescription monthly, then the prescription is stored in a secure location before collection. During this process, the pharmacist must also screen the prescription for clinical appropriateness.

In a busy community pharmacy, safety and efficiency are paramount. Authentication of medicines could occur at multiple stages in the dispensing process (**Table 2.0**). The scan could take place at the dispensing stage, the checking stage or the handing out stage. The majority of prescriptions in the UK are monthly collections and therefore prepared in advance which will influence where authentication takes place.

Table 2.0: A selection of advantages and disadvantages of authentication at the different stages of the dispensing process in community pharmacy.

Stage	Advantages	Disadvantage
Labelling stage	The terminal used to label the product may be used to perform the medicine scan, relinquishing the need for additional authentication terminals. Unsuitable medicines are identified early in the process. This provides the pharmacy with a better	Authenticating at this stage may slow down the labelling process by occupying a terminal for a longer period of time. If performed at this stage this task may be performed by a less qualified

	chance of procuring a replacement medicine to satisfy the patient's drug order, should the product in stock be identified as SF.	member of staff which may compromise the quarantine process.
Dispensing stage	Unsuitable medicines are identified early in the process, which provides the pharmacy with more time to procure a replacement medicine should the product in stock be identified as SF.	This staff grade may be less qualified to deal with SF medicines. Decommissioning at this stage may require a financial outlay for additional computer terminals for product decommissioning.
Checking stage	SF medicines are identified by highly trained registered professionals. Identification occurs closer to the patient, reducing the risk of a falsified medicine not being identified between the moment of authentication and the moment of supply.	SF medicines are identified at one of the last points before supply to the patient if the medicine is recalled and an alternative product is unavailable; this may disrupt patient supply. Medicines that are checked may be placed in storage for up to a month before collection, in which time a medicine could expire or be identified as recalled.
Handing out stage	Medicines are verified as safe at the final stage before reaching the public. Authentication technology can be configured to send alerts to the healthcare assistant, which facilitates patient education and counselling.	Medicines identified as unsuitable for the public at this stage may cause inconvenience to patients if there is no replacement stock available. This step would be carried out by the least qualified staff members which may increase the inadvertent supply of an SF medicine to a patient.

Regarding community pharmacy, the FMD is clear that medicines must be decommissioned at the point of supply to the patient. However, there is no clarity as to the exact stage of 'supply to the patient' that the final decommissioning will take place, and by whom. Decommissioning could take place at multiple stages within the pharmacy (**Table 2.0**).

2.2.2: UK Hospital Pharmacy

The complexities of hospital pharmacy are different to community pharmacy due to the operations involved in the movement of written drug requests from the wards to the pharmacy such as drug charts, inpatient request sheets, online requests and phone calls. Further complexities in a hospital pharmacy include robotics, hospital clinics and workflow complexities such as separate areas or rooms for preparing controlled drugs and extemporaneously prepared medicines. Furthermore, each hospital pharmacy has a different layout and work process, unlike large retail pharmacy chains which can often have identical layouts. Hospital pharmacies are necessarily tailored to the specialist needs of the hospital or trust both physically and operationally. The services that a hospital provides has an impact on the medicines a hospital pharmacy supplies, prepares or produces.

The actors in the dispensing process include the assistants who accept and conduct administrative prescription duties such as filing or tracking prescriptions, dispensers who process the prescriptions, pick the medicines for preparation and prepare these medicines with the appropriate labels. The final actors in this process are the accredited

checking technicians and pharmacists who check the product label and prescription for technical accuracy. Therefore, there are a variety of stages in the drug supply process where medicines could be de-commissioned (**Table 2.1**). Considering the assistant does not deal directly with medicines the possible actors in the dispensing process available to decommission or authenticate medicines are deemed to be the dispensers and the checkers.

Table 2.1: A selection of advantages and disadvantages of authentication at the different stages of the dispensing process in secondary care.

Stage	Advantages	Disadvantage
Goods in	SF products are identified upon receipt from the wholesaler and issues can be rectified early in the drug supply chain. The decommissioning process is completed without an impact on frontline services.	Scanning drugs by workers in the hospital pharmacy stores department would be a new process which may require further staff numbers to carry out the activity. After scanning at goods in, medicines may be recalled or expire. As they would not be scanned again before dispensing to a patient, this would increase the risk of supplying a patient with an expired, falsified or recalled drug.
Labelling	As per **Table 2.0**	As per **Table 2.0**
Dispensing	As per **Table 2.0**. Also, some hospitals have a process where labels are not produced until the correct medicine is scanned. Incorporating the scanning of the 2D data-matrix at this point adds no additional time to that process while complying with the EU FMD.	As per **Table 2.0**

Checking	As per **Table 2.0**. Many UK hospitals are familiar with scanning prescriptions at this stage to facilitate prescription tracking in the hospital. Therefore, scanning medicines at the same time could be incorporated.	As per Table **2.0.** Also, hospital dispensaries in the UK largely dispense for the same day and have less flexibility in managing their workload, unlike in community where monthly prescriptions can be dispensed in advance. Scanning drugs as part of the dispensing process may prove burdensome during busy periods.
Handing-out	As per **Table 2.0**. As hospitals deal with more specialist and rarely used medicines supplied to outpatients, it can be difficult to remember counselling advice associated with these medicines. A scan at this stage may generate drug information to remind staff of specific, less frequently used specialist medicines advice. Handing out of medicines within hospitals in the UK is often conducted by accredited checking technicians and pharmacists thus decreasing the likelihood of exposing less qualified staff to this task.	As per **Table 2.0.** An exception, lesser qualified staff, do not routinely hand out medicines directly to patients. Also, patients do not always collect medicines from the pharmacy department. Medicines can be collected by ward-based nurses or porters which further complicates the process.

2.3: An Analysis of the FMD and Hospital Pharmacy Sector

Since the publication of the FMD in 2011 and the subsequent delegated regulations (DR) in 2016, there has been much discussion around the level of FMD compliance required by secondary care institutions. Due to the complex nature of the secondary care drug distribution cycle, the FMD allows certain dispensations for ‘Healthcare institutions', this chapter reviews the FMD and delegated regulations to

understand and explain these dispensations and the impact of the FMD on secondary care.

The falsified medicines directive covers four themes, the supply chain, active ingredients and excipients, the internet, and product safety features. Product safety features include product serialisation with 2D data-matrix barcodes at manufacture, tamper evident seals for all products governed by the FMD, which includes the majority of prescription-only medicines and a minority of high risk over the counter medicines (18-19, 24, 27). The authentication of medicine occurring at the pharmacy or 'healthcare institution' level with a risk-based verification at wholesale level aims to prevent falsified medicines from reaching patients.

2.3.1: FMD Compliance in Secondary Care

The FMD is a safety tool for secondary care and compliance for all secondary care supply chain protagonists is mandatory – subject to a small number of exceptions when compared to primary care requirements. To understand the importance of authentication in secondary care in the UK, it is necessary to first understand the drug distribution cycle. Using the UK and the National Health Service (NHS) as an example (**Figure 2.0)** it is clear that the movement of drugs from the manufacturer to the hospital ward and corresponding patient differs between individual hospital sites within a single NHS trust and between European hospitals.

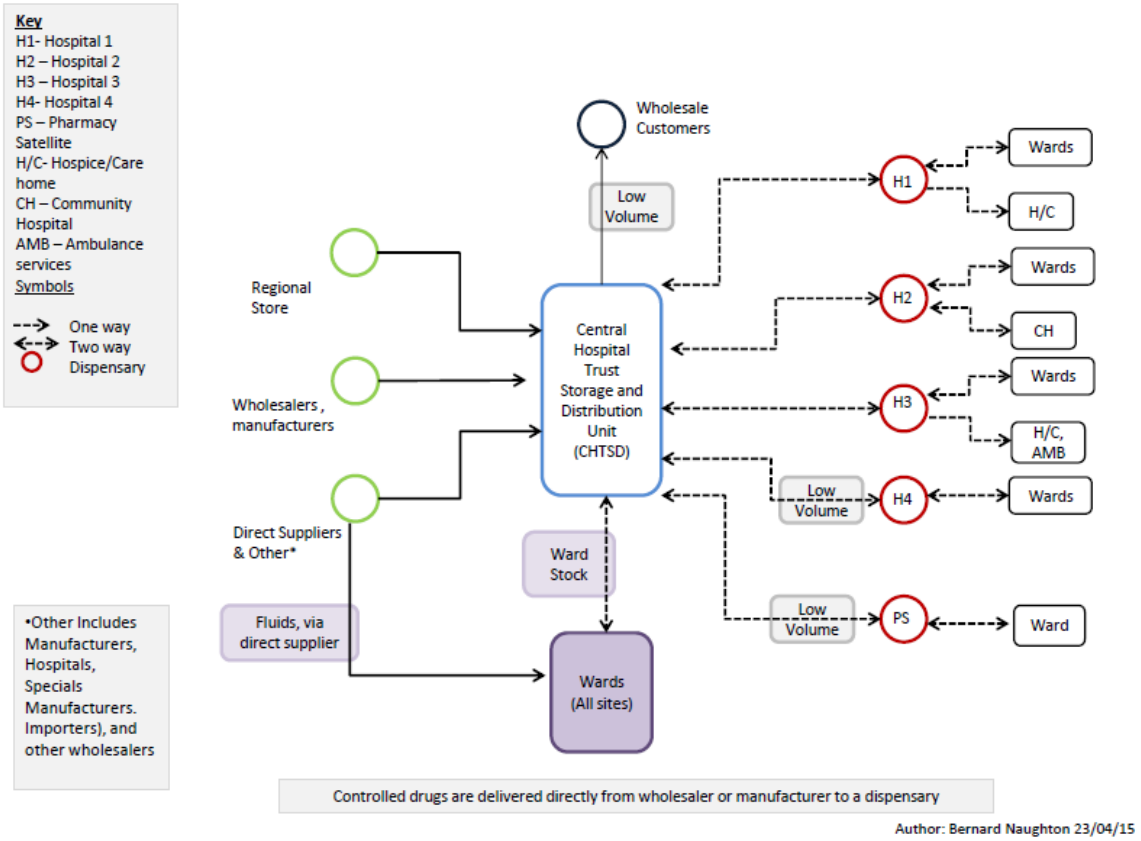


Figure 2.0: An exemplary UK (NHS) drug distribution cycle.

Sources estimate that a drug can travel through as many as 20 to 30 partners in the drug supply chain before reaching clinicians and the desired patient, making drug tracing challenging (93). Furthermore, many NHS trusts return unused medicines dispensed to hospital wards back into stock to control drug expenditure. Although this is a crucial move to manage finances and maintain the high level of healthcare that the UK has become accustomed to, this practice further complicates the drug distribution cycle in secondary care (**Figure 2.0**). The complexity of the drug distribution cycle within the NHS also poses challenges vis-á -vis most large NHS trusts hold a wholesaler dealing license. Having a wholesaler dealing licence permits each trust to routinely supply medicines to institutions such as community hospitals, hospices and the ambulance service not to mention the supply of scarce, time critical, medicines to other hospitals and community pharmacies in urgent circumstances; often out of normal working hours. These practices coupled with numerous drug entry points, via wholesalers, direct manufacturers and other suppliers create an entirely necessary yet convoluted drug distribution chain and environment which is open to the entry of illegitimate medicines. Such a distribution cycle is unparalleled in the primary care setting and creates an incredibly porous system with restricted transparency (93).

2.3.2: Mandatory FMD Secondary Care Requirements

Wholesaling Pharmacy Distribution Units

As highlighted previously many NHS organisations have wholesaler dealer licenses and as such are obliged to comply with FMD regulations regarding wholesale supply. According to article 23 of the FMD delegated regulation (DR) (page 21)(19), a Central Hospital Trust Storage and Distribution Unit (CHTSD) **(Figure 2.0)** with a wholesalers license would have to authenticate medicines before supply to certain persons or institutions, in a hospital setting this would more frequently be paramedics and emergency medical practitioners, universities, prisons, hospices and nursing homes rather than to other healthcare institutions such as hospitals.

Misconceptions: The Hospital Dispensation to Decommission

The draft DR published in August 2015 and final DR published in February 2016 contains details of the consultations prior to the adoption of the DR which describes most stakeholders as supportive of checking the unique identifier at the end of the supply chain, namely at community and hospital pharmacy level (19). Despite this support there is a special dispensation for "*specific institutions*" (page 9 point 23) (19) which could remove the obligation of safety feature verification to ensure that the verification measures on those parties 'is proportionate'(19). This phrase has caused widespread confusion and has led many to believe that hospitals are exempt from the FMD legislation. It means that specific institutions such as care homes, prisons and ambulance services are not required to decommission medicines.

Point 23 (page 9) of the DA (19) states that:

'It should be possible for the Member States to exempt specific institutions or persons authorised or entitled to supply medicinal products to the public from the obligation of verification of the safety features in order to accommodate the particular characteristics of the supply chain in their territory and ensure that the impact of the verification measures on those parties is proportionate.'

The DR states that 'specific institutions' may be exempt from authentication which does not necessarily equate to 'healthcare institutions' which specifically means a hospital, in- or out-patient clinic, or health centre (Point 2, Page 14) (19). However, the term 'specific institutions' is not explained further in either the directive or the delegated regulation.

Article 26 'derogations from Article 25' helps to further clarify this point, stating: '*Persons authorised or entitled to supply medicinal products to the public who do not operate within a healthcare institution or within a pharmacy are exempted from the obligation to verify the safety features and decommission the unique identifier of medicinal products where that obligation has been placed on wholesalers by national legislation in accordance with Article 23'*(19).

<u>Truths: Healthcare Institution Decommissioning Exemption.</u>

Within article 26 (derogations to article 25)(19), the DA sets criteria below, which, if met, would remove the requirements for healthcare institutions to authenticate (decommission).

'(a) The person authorised or entitled to supply medicinal products to the public obtain the medicinal product bearing the unique identifier through a wholesaler belonging to the same legal entity as the healthcare institution;'

Regarding secondary care environment, this would relate to the CHTSD (**Figure 2.0**) with wholesale dealers licence operating within the trust and therefore part of the same legal entity.

(b) The verification and decommissioning of the unique identifier is performed by the wholesaler that supplies the product to the healthcare institution;

In the case of secondary care, the 'Wholesaler' would be the CHTSD which would be responsible for authenticating or decommissioning the product before delivery to a specific hospital with the NHS trust in question.

(c) No sale of the medicinal product takes place between the wholesaler supplying the product and that healthcare institution;

The CHTSD ('Wholesaler') cannot sell decommissioned products to a hospital within its own trust. The CHTSD is permitted to 'supply' but not 'sell' a decommissioned product to a hospital within the same legal entity, i.e. a hospital within the same trust.

(d) The medicinal product is supplied to the public within that healthcare institution (19).

The decommissioned medicine would have to be then supplied to a patient in a hospital that is part of the same legal entity of the wholesaler (CHTSD). This restriction would disqualify any medicines

decommissioned by the CHTSD from being sold to other legal entities such as community pharmacies or other hospitals via a wholesale dealer's licence.

To qualify for an exemption to decommission a trust would have to receive its medicines via a pharmacy distribution unit department (CHTSD) or a similar variation of a CHTSD as per **Figure 2.0**. The CHTSD unit would have to perform the decommissioning and such a unit would have to hold a wholesaler's licence and form part of the same legal entity. As most NHS Trusts work via a CHTSD, and many have a wholesale dealers licence, this would be possible. The practice of decommissioning by the pharmacy CHTSD or wholesale level adds an extra step at the 'goods in' stage with little or no added clinical value. Information regarding expiry dates, recall status and suspicious medicines is dynamic. To revert to a system in which medicines are decommissioned at the 'goods in' stage totally detracts from the core principle of the FMD. The core of the FMD is that '*Persons authorised or entitled to supply medicinal products to the public should verify the authenticity and decommission a unique identifier at the time the medicinal product is supplied to the public so to access the most up-to-date information concerning the product and avoid that products which are expired, recalled, withdrawn or indicated as stolen are supplied to the public.'* point 24 (page 9) (19).

<u>Decommissioning Before the Point of Supply to the Patient</u>

The DA states that within the 'Healthcare institution' medicines may be verified before the point of supply to the public:

'*In order to avoid an excessive impact on the daily operations of healthcare institutions, it should be possible for the Member States to allow persons authorised or entitled to supply medicinal products to the public operating within healthcare institutions to perform the verification of the authenticity and the decommissioning of a unique EN 10 EN identifier earlier than the time the medicinal products are supplied to the public, or exempt them from this obligation, subject to certain conditions*' point 25 (page 9).

The quotation in the previous paragraph is an exception to the rule that '*Persons authorised or entitled to supply medicinal products to the public should verify the authenticity and decommission a unique identifier at the time the medicinal product is supplied to the public*' (Article 25, point 2, page 21).

If a healthcare institution does decide to decommission a medicine before the point of supply to a patient this can only occur *'provided that no sale of the medicinal product takes place between the delivery of the product to the healthcare institution and the supplying of it to the public'*. This restriction revokes the suitability of such medicines for wholesale supply, having an impact on the hospital wholesale business. To promote intra-trust and inter-trust movement of medicines it would make clear financial sense to decommission at the point of supply to a patient. This includes in the pharmacy for a patient-specific supply, or at ward level by a nurse. This ensures safety closer to the patient and allows flexibility for trusts to continue wholesale trading as usual.

‘The Ten-Day Rule’

For practical reasons the DR has permitted all pharmacies to revert the ‘decommissioned’ or ‘dispensed’ status of a drug to allow it be dispensed at a later stage if the conditions from Article 13 (point1 page 18-19) below, are fulfilled:

‘(a) the person performing the reverting operation is covered by the same authorisation or entitlement and operates in the same premises as the person that decommissioned the unique identifier;

(b) the reverting of the status takes place not more than ten days after the unique identifier was decommissioned;

(c) the pack of medicinal product has not expired;

(d) the pack of medicinal product has not been registered in the repositories system as recalled, withdrawn, intended for destruction or stolen and the person performing the reverting operation does not have knowledge that the pack is stolen;

(e) the medicinal product has not been supplied to the public’ (19).

The opportunity to reverse the decommissioning process facilitates the correction of decommissioning errors, with a ten-day window to perform this reversion which means that any medicine that decommissioned over ten days previous would not be suitable for sale. It is unclear why ten days was chosen as the deadline for re-commission medicines. However, the ‘Ten-day rule’ has a crucial part to play in establishing the most appropriate management approach to this regulation. The ten-day rule will not cause problems for pharmacies that dispense medicines via paper prescription from walk in patients. However, in the case of prescriptions prepared in advance this will cause disruption. In the UK for example

prescriptions are often done in advance of the patient collecting the prescription. Prescription can be done for up to three months prior to collection and if the patient does not collect the prescription and the product is not recommissioned within ten days, this could cause medicine wastage.

2.3.3: Where to Decommission Medicines in Hospital

The Point of Supply

The DA demonstrates (pg. 9 point 24) (19) that the verification of a product is not only to establish authenticity but also to inform the operator whether a product is expired, recalled, withdrawn or indicated as stolen using up to date information. It may take many months and, in some circumstances, years between a hospital receiving medicine and delivering it to a patient, in this time medicine may have expired, been recalled, or queries may have been raised as to its source. Therefore, to best utilise this dynamic information, the authentication of medicines as close to the patient as possible is a reasonable approach. Authenticity checks as close to the patient as possible provide certainty of safety up until the last moment that the medicine is supplied to the patient. Drug distribution is a complicated process, the further up-field that a check is performed the greater chance there is of bypassing the up-field check through alternative means. Checking at the point of supply or administration to a patient is the final, rate-limiting step and is less likely to be bypassed, therefore providing the most effective protection to the patient.

Regarding take-home prescriptions, the most effective place to authenticate might be at the point of dispensing; in terms of an in-patient supply, the safest place to authenticate would be at ward level before administration to the patient. This would provide a safety net for busy nursing staff and would work especially well with e-prescribing systems. Authentication could verify with the electronic prescribing system that the medicine selected matched the medication prescribed and that the medicine was not expired, or recalled, falsified or withdrawn. This is a model already being used in the US where we see the use of barcode eMAR technology. This model involves the electronic prescribing of medicines by medics, the clinical screening and ordering of medicines by pharmacists, the scanning of a patient's wristband and a drug being administered by the nurse. This process not only reduces prescribing and screening errors but the scanning of a patient's wristband and the drug packet caused non-timing errors in medication administration relative reduction of 41.4% ($P<0.001$)(94). If hospitals in the UK were to follow the US model and scan the FMD 2D data matrix, they could reach FMD compliance while reducing administration errors.

Regarding the FMD, whether it is a pharmacist in a dispensary or a nurse on ward level each member of staff must physically pick up each medicine container and check that they have selected the correct product. This checking process includes the checking of the contents of the container, the drug name, drug form and the expiry date of the product. Authentication or decommissioning at this stage would add 300 milliseconds (the maximum FMD authentication time and it is unknown

why this limit was chosen)). In fact, considering, the inclusion of tamper-evident packaging, reducing the need to open most medicine packs during the checking process, the FMD regulations will provide improved efficiency to current practice.

Medicines authentication services also have the capability to provide educational material when specific medicines are scanned which would be of great benefit in secondary care. This application could provide an onscreen injectable monograph to help nurses in the administration of intravenous drugs or provide key points to pharmacists counselling on rarely dispensed drugs saving time associated with using paper-based information which further supports the argument of scanning as close to the patient as possible. These opportunities to educate would only be possible if medicines were decommissioned at the point of supply.

Authentication at 'Goods In'

To authenticate at 'goods in' would remove all requirements for pharmacists or nurses to scan medicines at the point of supply and allow this directive to be implemented without an impact on frontline services. The disadvantage of managing this process at the goods-in stage, as mentioned previously is that medicines that were in date were not recalled or appeared un-suspicious at goods in, may prove to be dangerous between the time they are decommissioned and the point of supply to the patient.

Authenticating at the goods in stage would place the onus on distribution staff and would act as an entirely new step in the goods in process. This additional medicine handling and scanning process, would be a big change to practice as scanning is not routinely done at the goods-

in stage. There have been discussions surrounding the aggregation of 2D data matrix codes to permit the decommissioning of multiple packs at once. The creation of aggregated codes will be set up to benefit large pharmaceutical wholesalers and is unlikely to deliver the same benefits to a CHTSD, due to lower and more sporadic ordering volumes. It is not always the case that medicines are distributed to hospitals in unbroken parcels or palettes, which would largely require the decommissioning of each individual medicine packet, a practice that would likely require the creation of further posts and financial outlays in an already financially constrained health care system. Unlike authentication at the point of supply, where useful up to date information regarding the status of the drug (expired, recalled, suspicious, product shortage, reimbursement status, or healthcare pop-up advice) is provided, decommissioning at the 'goods in' stage offers little or no advantage to distribution staff. With no information incentives to prevent clinical errors during decommission, compliance by distribution staff may not be as effective as those seen at the point of supply to the patient.

There are some safety and management issues associated with decommissioning at the 'goods in' stage in terms of rare and time-critical medicines. A hospital may be in possession of a critical medicine, however, due to its decommission ten days previously the new directive would not permit its wholesale supply to another trust in an emergency situation, which may put a patient lives at risk. The decommissioning of products at the point of supply would alleviate this issue as medicines would only be decommissioned when supplied to a hospital ward or

patient. Therefore, medicines within the dispensary or CHTSD would always be available for wholesale as they would only be decommissioned upon exit from either area. The alternative would be to create a two-stream system where a certain percentage of medicines were decommissioned at goods in and others decommissioned at the point of supply to the patient. A system of this description would be possible but could prove difficult to manage and may cause internal confusion.

Implementing the FMD in the Hospital Context

Contextual understanding is a concept that is often referred to in social sciences to describe an environments attributes and the effect of these attributes upon the outcomes of change. The contingency theory (95- 96)) postulates the context phenomenon. This theory explains that it can be observed and measured whereas other theories such as Burrell, 1994 (97) argue that context is probably not quantifiable and some argue that it is a socially constructed phenomenon (98).

Regarding implementing regulatory driven innovations in healthcare, context plays an important role. As described above, hospitals do not employ a linear approach to operations. The modern UK healthcare system promotes the advent of tertiary referral centres. Specialist services are increasingly shifting from the district general hospital environment to the large teaching hospitals. In terms of secondary care, context differs based on staff quality and number, workload, technological advances, specialist services, management structures and approaches. When deciding on the optimum point to decommission it is worth considering how secondary care nuances mentioned previously, such as robotic

dispensing, ward-based dispensing, split packs, satellite pharmacies, aseptic production and ward stock supply processes might be managed within the regulatory and practical constraints of the FMD.

There are some legal, practical and safety reasons which justify authentication as close to the patient as possible. However, the context within each hospital is likely to differ which will inevitably impact the uptake and compliance of authentication both locally and at a national level. Three broad dimensions of context are suggested by Dopson et al. (98) macro, meso and micro contexts. Regarding information technology projects within the NHS, macro-level contextual factors include high level financial, policy and regulatory issues which require debate and decision before implementation can take place. The costs and time taken to reach decisions at a macro level are likely to influence the opportunity to effectively manage micro contexts which will ultimately threaten the successful implementation of an information technology project within a given context. As there is a firm European deadline of February 2019 if key decisions such as choosing an authentication provider or adapting individual hospital operations are not made well in advance, this will result in severe pressure on front-line staff and a rushed implementation agenda. The success of implementing an innovation such as medicines authentication, (although an EU-wide agenda) principally affects a single department within a hospital or trust and will, therefore, rely largely on the consideration of meso and micro contexts within the hospital to facilitate implementation or roll-out.

Ferlie et al. (99) mentions that good relations between professional groups and active networking with university and professional institutions and a pro-research culture are positive micro contexts involved in the adoption of a policy, whereas negative micro contexts include power struggles and disengagement by a key stakeholder. Ferlie et al. mention that ‘soft management' from well-placed clinicians can be an effective way of persuading professional colleagues to change traditional working practices' Ferlie also mention the importance of a multidisciplinary team in breaking down professional boundaries. It is therefore anticipated that a well-funded, pro-research hospital attached to a University is more likely to be more successful with FMD implementation that smaller less forward-thinking hospitals.

2.4: Conclusions

This chapter conducted an in-depth analysis of the FMD, and its effect on the hospital pharmacy sector. It has also identified the dispenser and either accuracy checking technicians or pharmacists as suitable staff for the decommissioning of medicines. This chapter analyses hospital pharmacy workflows compared to the community pharmacy sector workflows and demonstrates the regulatory, legal, practical and safety justifications for medicine decommissioning as close to the patient as possible in the UK. Considering the authentication of medicines has been occurring in community pharmacy for a number of years (in Belgium, Italy and Greece) and the additional operational complexities of the hospital sector it is recommended that a medicines authentication study is conducted in a secondary care setting initially. A study in a hospital setting

is required to address concerns, which include the technical and operational effectiveness of the approach, the key point in the dispensing process to authenticate and improvements which may facilitate an effective implementation. Oxford University Hospitals NHS Foundation trust and more specifically the Horton Hospital, due to its varied services and experienced staff is a suitable study site to make these assessments. It would also be appropriate to observe the context of the hospital and study implementation to identify meso and micro contexts which may affect health information technology implementation or technology uptake within the hospital and further identify and investigate management concepts and strategies to improve innovation implementation and adoption. Chapter three will investigate the FMD mandated DMST in a live environment, assessing both technical and operational performance of the approach.

Note: The majority of this chapter has been published in the following outlets:

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Naughton BD. The EU Falsified Medicines Directive: key implications for dispensers. Med Access @ point care 2017; 1(1): e155 - e159

3.0: The Quantitative Analysis of a Manual Medicine Screening Technology in Secondary Care

3.1: Introduction

The current methods for detecting falsified medicine, are varied and span from laboratory-based methods through to SMS texting with most detection being conducted by customs officers at international borders, using the former approach. Technology in drug detection has advanced, and many techniques are now available which include spectroscopy, chromatography, SMS, hand-held or portable laboratories, radiofrequency identification and serialisation (100) All of these techniques have been discussed in detail in chapter one. Serialisation is the process of identifying a medicine with a unique code printed onto the medicines pack and verification is the process for identifying and checking that code. Regarding the FMD, the term 'authentication' relates to the final scanning of medicine and the subsequent decommissioning of a product at the point of supply to the patient to ensure authenticity. The 2011 FMD (18-19, 24, 101) and the 2013 DSCSA (102) have adopted the serialisation and verification approach for substandard and falsified (SF) medicine detection. This serialisation and verification process is a low cost, non-destructive and quick method for detecting counterfeit medicines. The FMD requires the systematic authentication of medicines at the point of supply to the patient while the DSCSA requires verification at every point of sale and exchange throughout the drug distribution cycle, currently without authentication at the point of sale or administration to the patient. Although practices similar to those proposed by the FMD exist

within the Italian, Greek and Belgian primary care markets, principally as a reimbursement method, FMD legislated serialisation and authentication technologies are alien to many countries. Furthermore, they have not been academically assessed and may prove challenging to implement, especially in the complex secondary care environment for reasons explained in chapter two (103). This chapter describes the piloting of the FMD mandated medicines verification technology and the associated processes. This pilot assesses the effectiveness of this technology and highlights issues which require resolution before the 2019 FMD implementation deadline.

3.2: Methods

The objectives chosen below aimed to assess the technical and operational effectiveness of the digital medicines screening or authentication technology and the following measures were used to measure effectiveness.

OAR	Operational Authentication Rate: The number of medicines scanned by staff as a percentage of those entered into the study i.e. staff scanning compliance
ADR	Absolute Detection Rate: The number of medicines quarantined as a percentage of those entered into the study with quarantine alerts
ODR	Operational Detection Rate: The number of medicines quarantined as a percentage of those identified as requiring quarantine by the technology i.e. staff quarantine compliance in response to alerts
RR	Response Rate: The time taken to send data from a medicine scan to an external database, for that data to be verified and for a response to be returned to the scanning terminal. The FMD limit is 300 ms.

Primary Objective

- To identify the OAR, ADR and ODR of medicines authentication technology in the secondary care environment.

Secondary Objectives

- To identify the optimum point in the dispensing process to authenticate medicines based on OAR and ODR's.

- To identify an average RR for this study.

3.2.1: Study Site

The district general hospital involved in this study is one of four hospitals in a large UK national health service teaching foundation trust. As explained in chapter two this site was selected due to the presence of both specialist and general medical and surgical services provided. The variety of clinical services available ensured a diversity of medical treatments in hospital circulation and provided a balanced portfolio of medicines available for serialisation during this study.

3.2.2: Methodology

A literature review was conducted using 'Google Scholar', PubMed' databases' and online grey literature to understand if medicine verification pilots or studies had been conducted to estimate the effectiveness of the medicines authentication approach. Much of the work in this area existed in grey literature. Studies reported in the grey literature often did not contain explanations of the methods used to conduct these studies and do not use live serialised medicines. As the initial number of recalled, expired or suspicious medicines in the samples of these studies

are not known from the outset, it is difficult to assess the effectiveness of the detection approach. Without knowing the number of illegitimate medicines within the system initially, it is not entirely possible to test the effectiveness of the approach. Instead, tests have been conducted with codes which have known responses. This does not reflect the reality of scanning in a busy healthcare environment and does not provide an insight into the obstacles faced during authentication on a daily basis. The approach seen in these studies do not take into consideration the prevalence of any medicines that may have slipped through the system through poor rate of staff scanning or issues relating to poor stock control. One study by Simoens et al. (104) goes some way to answer these questions. The Simoens et al. (104) study involved existing serialised medicines within Belgium, which were scanned by community pharmacists for reimbursement purposes. This study aimed to identify the reliability of the authentication technology to correctly identify medicine as either authentic, expired, recalled or suspicious. The method used by Simoens relied on a mystery shopper entering the pharmacy and asking the pharmacy to authenticate their drug. This included 1309 medicine packets presented by multiple mystery shopper encounters to 116 Belgian pharmacies. The first limitation of this study relates to the low number of medicines scanned. This paper does not explain whether or not the patient presentation of medicine for scanning is common practice in this context. If this is an unusual request this may have heightened the pharmacies awareness and increased compliance with procedures and awareness to technology alerts. Authenticating a medicine at the request of a patient is

a much different action to the passive authentication of medicines as a part of routine dispensing practice. As this study does not reflect the anticipated process post FMD implementation, it does not answer key questions such as operational authentication rates and other issues which may arise in a live dispensary environment. By knowing the outcome of each barcode, the researchers could understand how accurate the medicines authentication approach was by matching the result provided by the pharmacist with the true status of the medicine. Although this study assessed the technical effectiveness of the approach, it did not assess the operational effectiveness or highlight any potential issues which may arise as a result of the FMD, i.e. medicine authentication at the point of supply to the patient. Considering the limitations of the approach taken by Simoens et al., a new method was created. The method used in this study was unique to this study and was designed by the lead researcher.

3.2.3: Study Set-up

It was important that the number of medicines entered into the study was tallied with the numbers authenticated by the staff and the number quarantined to understand weaknesses within the pharmacy dispensing end of the pharmaceutical supply chain. Entering medicines known to be recalled, expired or suspicious into the legitimate supply chain presented ethical and safety challenges, because if they were not identified during the study screening process they would enter the supply chain. Therefore, two dimensional (2D) barcodes were created which were pre-programmed with a message to identify a medicine as expired, recalled or authenticated elsewhere. All medicines included in this study

were to the best of the researcher's knowledge safe for administration. This approach was anticipated to satisfy the need to reconcile medicine numbers throughout the supply process without introducing expired, recalled or falsified medicines into the supply chain.

3.2.4: Sample Selection

Medicines were selected using a set of inclusion and exclusion criteria (**Figure 3.0**). These criteria ensured that the medicines selected for inclusion reflected the categories of medicines governed by the FMD and the most commonly falsified drug groups, which included the top 50 medicines by turnover and the top 50 medicines by cost at the study hospital site. Duplicate products and medicines not covered by FMD legislation were then excluded. This process returned a list of 87 products. The top 15 by usage and top 15 by value were then included in the study. A reduced number of study products was implemented for practical administrative reasons (**Appendix 1.0**) This approach is taken to ensure the sample of study medicines was diverse and represented the major clinical indications and formulations (**Appendix 2.0**). This approach ensured that a variety of products of differing clinical indication, formulation and cost were included in this study, and therefore, represented the variety of medicines used in the secondary care environment, and avoided the excessive inclusion of medicines which are not governed by FMD legislation. An exception was made for some high-volume P and GSL medicines in an effort to maintain high study medicine dispensing throughput.

Inclusion criteria	Exclusion criteria
• Licensed medicinal products • POM, P + CD medicine categories • Listed on site PMR in top 50 (by transactions or value)	• Unlicensed medicines • Clinical trial material • GSL Medicines • Medical device without drug component • Medicines not issued directly to a patient including ward stock, fluids, TTO packs • Fertility/Homecare medicines • Contrast media

Figure 3.0: Inclusion and exclusion criteria for the chapter three study medicines.

3.2.5: Materials

The global standards one (GS1) two-dimensional (2D) data matrix labels were produced and cut to size to limit the product area obscured by the label. Corresponding 2D data matrix codes were loaded and stored in an excel spreadsheet. The authentication technology was integrated into the hospital patient medication record (PMR) by creating an interface between the PMR and authentication software. This interface allowed an operator to scan a drug while in the PMR system to verify its status against a database of known to be safe medicine codes. The DMST software was operated by an existing computer terminal. The medicine codes were presented as a 2D data matrix and scanned using a handheld, terminal powered, barcode scanner. This process identified the product as either 'authenticated elsewhere' (falsified), 'item expired', 'item recalled (product or batch)' 'authenticated' or 'already authenticated here' (**Figure**

3.1 and **Figure 3.2**). A further description of the methods can be found in the research protocol in **Appendix 2.0**.

3.2.6: Labelling Procedure

Each 2D barcode was listed in an excel database. Drug details such as product name, form, strength, pack size, and the date the product was labelled was recorded in the database when the adhesive code was adhered to each study medicine, providing a complete record of study medicines serialised and the date of inclusion into the study. The 2D data matrix was attached to each study product according to a hierarchy of position described in the study protocol to ensure that the obscuring of important clinical data such as product name, strength form, batch number or expiry date was not excessive during the study period.

2D data-matrices were attached to all study medicines each Monday and Wednesday between the hours of 07:00 and 14:00, weekly. This maintained the serialisation of product lines throughout the study. 96% of medicines labelled, once authenticated by the operator would provide an on-screen symbol to indicate the product as safe for use and 'authenticated'. If a product authenticated within the organisation were to be re-authenticated, the system would display an 'already authenticated here' message **(Figure 3.1)**. This 'authenticated here' message was useful when dealing with multiple authentications of split pack medicines. Both 'authenticated' and 'already authenticated here' messaging did not require quarantine (**Figure 3.1**). One percent of medicines were labelled with a 2D data-matrix which generated a pop-up message of 'Authenticated elsewhere' (**Figure 3.2**) indicating that this drug may have been

counterfeited or falsified (copied) and introduced or re-introduced into the legal supply chain. A further three subgroups were introduced into the study, classified as recalled packs (1%), recalled products (1%) and expired products (1%) at a frequency of one percent per subgroup (**Figure 3.2**). All study products which were labelled with a 2D data-matrix, generating a warning popup message had the expiry and batch number recorded in the excel database upon inclusion in the study to facilitate follow up, should any of the study products require subsequent investigation. The 1% figure used in this study was based on the World Health Organisation (WHO) estimates that approximately 1% of the medicines in high income countries are falsified (16). To ensure equity amongst subgroups the expired medicine and recalled medicines groups were also allocated a 1% distribution.

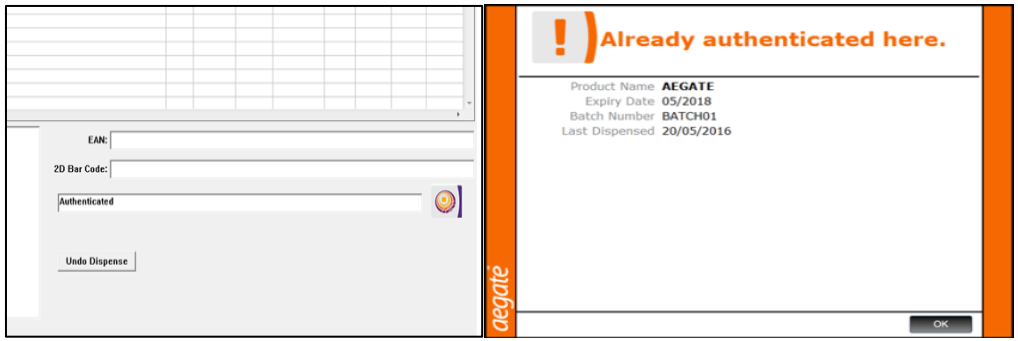


Figure 3.1: Pop-up messages triggered upon authentication of medicines that do not require quarantine.

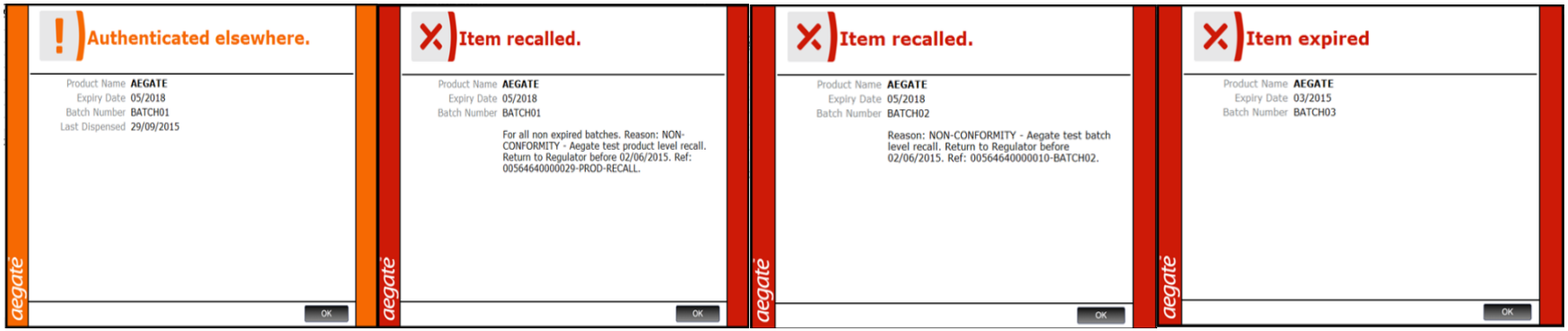


Figure 3.2: Pop-up messages triggered upon authentication of medicines requiring quarantine.

3.2.7: Study Design

A two-week pilot was conducted initially to ensure the technology and proposed study process was practical and without external database communication issues. The study was then separated into two parts. Stage one involved the authentication of medicines at the checking stage (by pharmacists and accredited checking technicians) and stage two at the dispensing stage (by dispensers and some accuracy checking technicians) according to the authentication protocol in **Appendix 2.0**.

All staff were subjected to the same basic training (presentation and demonstration) and were instructed to authenticate according to the authentication protocol. Operators authenticated medicines at the point of supply to the patient or ward for named patients. Ward stock authentication was not included in this study. Data cleansing and analysis was conducted for authentication and detection data using a cleansing and analysis form (**Appendix 3.0**). This form was independently checked by a second researcher to confirm study results.

3.2.8: Statistical Analysis

Drug sample size studies were conducted to ensure the total sample of study drugs was large enough to obtain acceptable confidence intervals and margins of error using sample size calculations (105). The total population was based on 2015 average eight-week dispensing figure of 9605 products, and the sample sizes were 2115 (stage one) and 2077 (stage two). Percentages were used for normalisation. To demonstrate a significant difference between the outcomes in stage one (checkers) and

stage two (dispensers), Chi-squared tests and Fisher's exact tests were used. Both tests are suitable for nominal data however Chi-squared test is suitable for sample sizes greater than 1000 and fishers test is best suited to smaller sample sizes. A p value of <0.05 was deemed as being significant, and confidence intervals of 90% were used throughout (106).

3.2.9: Operator Groups

Stage one contained a selection of pharmacists and accredited checking technicians. Stage two contained a selection of dispensers and accredited technicians. Dispensers could not be involved in stage one by law and pharmacists would not routinely be involved in stage two due to departmental policy; dispensing is not a role conducted by pharmacists during normal working hours, and this hospital did not provide an out of hours on-call service based at that site. Accuracy checking technicians are largely responsible for involvement in stage one and there are likely to be instances where they would also be involved in stage two. However, this is standard practice across the UK. No one person was permitted to be involved in both stages for the same prescription according to hospital policy.

3.2.10: Blinding and Disclaimers

Operators: Although the 2D labels contained some adjacent print, which if analysed carefully over numerous scans could reveal a trend between expired and recalled medicine labels, to do so would be very time consuming, unlikely to have occurred and was not mentioned in operator feedback. The operators were blinded as to which drugs were falsified, expired or recalled. The researcher was not blinded at the point of

labelling. As authentication was performed towards the later stages of the prescription preparation process, authentication had no part to play in stock control during this study. The study did not relate to or use any patient data.

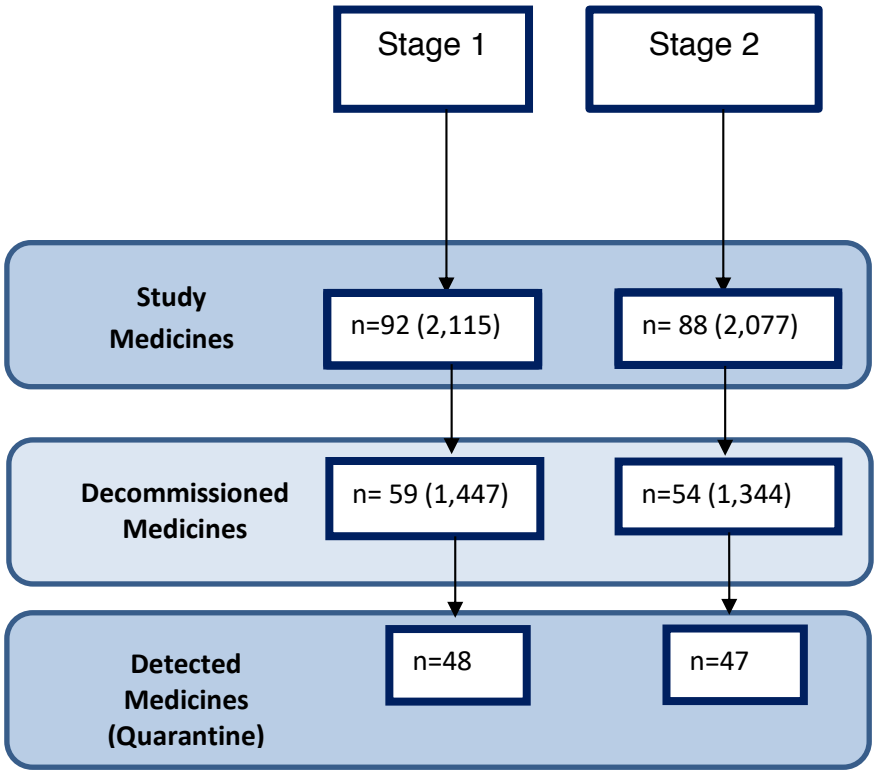
3.2.11: Patient Involvement

Patients, carers or laypersons did not participate in this research. The design of this study, the research questions and the outcomes measures, were informed by clinical, technical, research and industry leaders and did not include patient involvement. Clinical, technical, research and industry leaders were involved in the recruitment to and conduct of this study. Results will be disseminated to study participants through internal presentation and access to the research manuscript once available. Participants have been acknowledged in publications where applicable. Further information regarding the methods used in this study can be found in the study protocol (**Appendix 2.0**).

3.2.12: Ethical Approvals

This study was classified as a service evaluation study according to NIHR guideline's and agreed by PhD supervisors; as such did not require ethical approvals.

3.3: Results



Key

n= Number of study products containing error messages

(...)= Number of total products entered into the study

Figure 3.3: Flow diagram which identified the total number of medicines serialised for each stage of the study (study medicines), medicines scanned by the authentication technology and cross checked against the secure database (decommissioned medicines) and the total number of medicines in each stage quarantined for researcher investigation (detected medicines).

A total of 4,547 drugs were entered into this study, (2,115 in stage one; 2,077 in stage two) 180 of which contained a pre-programmed message popup which described the product as either authenticated elsewhere (falsified), expired or recalled and requiring quarantine (92 in stage one, 88 in stage two) (**Figure 3.3**). The stage one group

authenticated 1,447 medicines of which 59 required quarantine. The stage two group authenticated 1,344 medicines, of which 54 required quarantine. Not all medicines that were identified as requiring quarantine were quarantined. Only 48 of the 59 medicines in stage one and 47 of the 54 medicines in stage two were quarantined.

Table 3.0: Numerical representation of OAR, ADR and ODR percentages.

Parameter	Stage One Checkers	Stage Two Dispensers	Difference
Operational Authentication Rate (OAR)	68.4% (66.8-70.1)	64.7% (62.9-66.4)	3.7% (1.4-6.2) p<0.05 (Chi squared test) (107)
Operational Detection Rate (ODR)	81.4% (73-89.7)	87% (79.5- 94.6)	5.7 % (-5.55 to 16.9) (109) P=0.15 (Fishers Exact Test) (109)
Absolute Detection Rate (ADR)	52.2% (43.6-60.7)	53.4% (44.7-62.2)	1.2% (-11 to 13.5) P=0.12 (Fishers Exact Test) (109)
90 % Confidence Intervals were used throughout (110) (108)			

The OAR relates to the number of medicines authenticated in a particular stage as a percentage of the total number of medicines entered into the stage. For this study, the OAR was 66.3% overall, 68.4% (66.8-70.1, 90% CI) (Stage one) and 64.7% (62.9-66.4, 90% CI) (Stage two) (**Table 3.0**). There were no technical issues observed with technology. The ADR demonstrates the ability of the authentication process

(technology and operator) to detect a counterfeit, expired and recalled medicine, i.e. taking into consideration the human operator and the complex hospital environment that the technology operated within. 95 of the 180 medicines requiring quarantine were quarantined, 48 (52.3%) in stage one and 47 (53.4%) in stage two. This demonstrates a difference in ADR of 1.2% (-11 to 13.5, 90% CI, p=0.12) between the groups. The ODR demonstrates the relationship between medicines identified as falsified, recalled or expired by the technology and those correctly quarantined by the staff. The ODR was 81.4% (73-89.7, 90% CI) in stage one and 87% (79.5- 94.6 90% CI) in stage two. This was a 5.7% (-5.55 to 16.9, 90% CI, p=0.15) difference between the groups.

Table 3.1: Breakdown of medicine subgroups and detection throughout the dispensing cycle.

Medicines Included	**Authenticated elsewhere(Falsified)**	**Product Recalled**	**Batch Recalled**	**Item Expired**
Stage One	22	24	24	22
Stage Two	22	22	22	22
Database Detection	**Authenticated elsewhere**	**Product Recalled**	**Batch Recalled**	**Item Expired**
Stage One	13	12	18	16
Stage Two	11	17	12	14
Operator Detected	**Authenticated elsewhere**	**Product Recalled**	**Batch Recalled**	**Item Expired**
Stage One	7	12	13	16
Stage Two	7	16	12	12

There were five groups of drugs, with five corresponding pop-up messages entered into this study, falsified drugs (authenticated elsewhere), recalled products (product recalled), recalled batch (batch recalled), expired medicines (item expired) and safe to use medicines (authenticated). Across both stages, 31.8% of falsified medicines, 58% of

recalled drugs (product and batch) and 64% of expired medicines were detected (ODR) (**Table 3.1**).

Table 3.2: Z-test outcomes for ODR in each subgroup.

Subgroup	Falsified (Authenticated Elsewhere)	Pack Recalled	Expired	Product Recalled
Counterfeit (Authenticated Elsewhere)		Yes	Yes	Yes
Pack Recalled	Yes		No	No
Expired	Yes	No		No
Product Recalled	Yes	No	No	

Z tests by proportion for independent groups identified if the differences between ODR in each subgroup were significance (**Table 3.2)** (Yes or No outcomes were generated using **Table 3.1** data). There was a statistical difference between the counterfeit group and all other subgroups, both individually and as an entire group, this means that the percentage of medicines in the falsified drug group detected was significantly lower than those in the other groups (recalled and expired). An image of the authenticated elsewhere (falsified, requiring quarantine) and authenticated here (not requiring quarantine) are represented in **Figure 3.4**.

Figure 3.4: Pop up message warnings which are generated when a falsified medicine (left) and a medicine which has already been authenticated on site (right) are scanned.

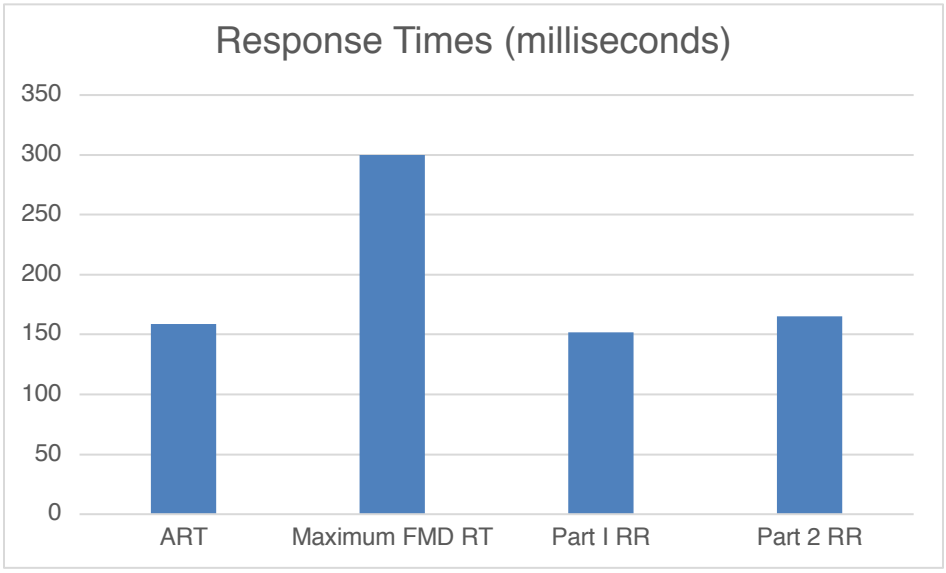


Figure 3.5: Average response times versus FMD response time limits.

The medicines authentication technology response rate (RR) is the total time taken for the information scanned from the 2D data matrix to make a round trip from the scanning terminal to the authentication database and back. The mean response time over each eight-week period was 152 milliseconds in part one and 165 milliseconds in stage two (**Figure 3.5**). The FMD mandated response rate is less than 300 milliseconds (18).

3.4: Discussion

Medicines were entered into an active secondary care dispensary system. The data generated (**Figure 3.3** and **Table 3.0**) identified a gap between serialised medicines entered into the system and those identified by the authenticating technology, the operating authentication rate (OAR). There also appears to be a disparity between medicines identified as requiring quarantine by the technology and those separated for quarantine (ODR) (**Figure 3.3**). The OAR which represents user compliance across both stages was 66.3%. When compared to the expected standard of 100% this figure appears to be relatively low, however, this figure should be considered in light of the novelty of the technology, the frequent problems encountered in technology implementation projects within the NHS (111) (112) and the lead time to legal compliance. The OAR demonstrated a statistically significant difference of 3.7% (1.4, 6.2, 90% CI, $p<0.05$) between stage one and stage two, which consisted of two largely different operator groups. A 3.7% difference in authentication rates could lend itself to the argument that the pharmacists and accuracy checking technicians at the checking stage are more adept at manual medicines authentication at the point of checking than their dispenser counterparts at the point of dispensing. This difference could be due to the professional registration obligations of the operators in stage one and professional good practice which protects the staff involved in stage one from interruption during the medicines checking process. However, once the FMD compliance deadline of February 2019 is reached staff will be legally obliged to authenticate medicines and failure to do so will be against the law.

Although it has not been made clear by UK regulatory authorities it is likely to be classed as a dispensing error and treated in the same way.

There were no concerns raised during this study regarding the technical solution. Although stage one data demonstrated an ADR lower than stage two, a difference of 1.2% (-11 to 13.5 90% CI, p=0.12) relating to sample sizes of 59 (stage one) and 54 (stage two) was identified by a Fisher's exact test as non-significant p=0.12. It was observed that even when the technology identified a drug to be falsified, recalled or expired the staff across both stages did not always quarantine that medicine. ODR rates demonstrated a non-significant 5.7 % (-5.55 to 16.9, 90% CI, p= 0.15) difference between stages. Therefore, one group could not be described as 'better' than another in this study, in terms of operational detection rates. Despite the lack of statistical significance between groups, there is a clinical significant difference between the overall group (stage one and two combined) in terms of ADR and ODR compared to the expected legislative detection rate of 100% (**Table 2.0**). Detection rates appear to be influenced by two main factors, the compliance of staff in the authentication of medicines (OAR) and increased awareness to messaging which identifies a medicine as falsified, recalled or expired (ODR).

There was a total of 92 (stage one) and 88 (stage two) medicines, containing quarantine messaging, introduced into this study (**Figure 3.3**). These figures included a collection of medicines which varied in their pre-programmed messages to include; authenticated elsewhere (falsified), product recalled, batch recalled and item expired (**Table 3.1**). Across both stages, 31.8% of counterfeit medicines, 58% of recalled drugs and 64% of

expired medicines were detected (**Table 3.1**). There was no demonstrable difference between stage one and two for any of the subgroups in **Table 3.1**. As a total group, however, there is a difference between the ADR rates for the 'authenticated elsewhere' subgroup (31.8%) and those of other subgroups (60%) (*Z*-test) (**Table 3.2**). This is likely due to confusion between the 'authenticated elsewhere' and 'already authenticated here' messages which are similar in terms of message content and colour (amber) (**Figure 3.4**), with the former requiring quarantine and the latter requiring no action.

The Response Rate (RR) is the time taken to send information to an external database, cross-check and retrieve a reply which states the status of the drug. The RR was 152 milliseconds (stage 1) and 165 milliseconds (stage 2) (**Figure 3.5**) over 2,791 scans, which is appropriate for systematic authentication of medicines when compared to the accepted FMD regulatory limit of 300 milliseconds (18-19). This data is however based on a relatively small sample and may not necessarily be repeated in the presence of a larger throughput of medicines scanned through an NMVS. This response rate would require regular assessment once this technology is implemented nationally and internationally. If the electronic system goes offline the pharmacist has the option to supply the medicine and verify the code at a later stage. This would be a difficult situation for a pharmacist to be placed into. Therefore, it is important to keep response times quick and offline issues as infrequent as possible. There is currently no UK information regarding how the GPHC or the MHRA will deal with poor authentication compliance.

3.4.1: Study Positives and Negatives

There was some participant group crossover in this study; however, this is standard practice in UK NHS hospital dispensaries, reflecting normal working patterns in the medicine supply process. This study was carried out in a single hospital, and therefore, similar studies in a number of other UK hospital sites could adopt the present study design and replicate the work to identify whether the results of this study are indicative of the entire NHS environment. Due to the emerging nature of this technology, there have been no other studies in this field to compare results. In addition, this study included a large sample of study drugs which generated results large enough to demonstrate statistically significant outcomes for some parameters.

3.5: Conclusions Context and Impact

Government organisations such as the Federal Bureau of Investigation (US), the Internal Revenue Service (US) and the National Health Service (NHS) (UK) are no strangers to information technology project failures (113). The NHS in the UK has experienced a recent struggle with the national programme for information technology (NPfIT), which required the implementation of the electronic patient record by 2005 (a target set in 1998). By the spring of 2002, only 2% of trusts had reached this target (111-112). The government then ring-fenced the information technology budget and pledged £2.3bn to NPfiT with the aim of implementing electronic patient records by 2007. Electronic patient records are yet to be completely rolled out across all NHS trusts. FMD

rollout will happen at all pharmacies around the UK in February 2019. Some of the failing associated with the NPfiT project related to poor stakeholder involvement. It is important to include stakeholders during FMD roll-out to avoid failure in implementation.

It is important to understand the role that context plays in implementing healthcare innovation. Each hospital will have a different context which will affect innovative implementation, and it is important to understand the internal and external context that facilitates the successful implementation of healthcare technology (114-115).

This study involved the presentation and the dissemination of a protocol to the participants. Carthy et al. (116) raises concerns regarding the growing number of protocols and guidelines which require attention by NHS staff, which in this case may also have a part to play in non-compliance. It is therefore important to understand that protocols alone are not adequate when introducing technology into a complex environment (103) and to instead use for interactive methods of education staff.

The more specific issue of pharmacy healthcare professional non-compliance can also be seen in a study by Thomas et al. in 2016 (117) which conducted qualitative interviews to understand the reasons for pharmacy non-compliance to procedures. Reasons for non-compliance included work demands, high workload and the social norm within the pharmacy. Staff felt like they were unable to follow procedures due to lack of staff, the pressure to reach targets and poor communication. Therefore,

adequate funding is required to ensure pharmacies have the resources they need to implement FMD roll-out.

Another factor which affects adherence to processes is the use of pop up reminders by authentication technology providers. Pop-ups and alerts in healthcare are commonly seen in electronic prescribing systems. Shojania et al. (118) has conducted a systematic review of evidence for the benefits of pop-ups and demonstrated a 4.2% increase in adherence to processes across all studies (interquartile range 0.8-18.8%). Shojania then goes on to say that an increase in adherence was much smaller than those expected. In cases where action was required following the alert the level of improved adherence increased to a median 12.9% [IQR 2.7%– 22.8%] v. 2.7% [IQR 0.6%–5.6%]; p=0.09). Although Shojania explains that this difference may have been confounded by exceptional practice in a particular hospital, it suggests that it is worth considering the inclusion of a rate-limiting "action taken field", to facilitate improved adherence to an authentication protocol.

Medicines verification technology is an approach which aims to safeguard EU and US citizens against falsified, expired and recalled medicines. The potential shortfalls of this technology should ideally be addressed before the EU (2019) and US (2023) regulative deadlines. Further qualitative research is required to understand the contextual reasons for less than optimum authentication and detection rates. It is key to investigate the technology, process, and educational adjustments required to improve the authentication and detection rates demonstrated in this study which in turn would improve patient safety. Chapter four

proceeds to investigate DMST user opinion and aims to identify ways to improve the quantitative results seen in chapter three.

Note: The majority of this chapter has already been published in:

Naughton B, Roberts L, Dopson S, Chapman S, Brindley D. Effectiveness of medicines authentication technology to detect counterfeit, recalled and expired medicines: a two-stage quantitative secondary care study. BMJ Open. 2016 Dec 1;6(12):e013837

4.0: A Delphi Method Study to Establish Expert Opinion on Digital Medicine Screening Technology in Secondary Care

4.1: Background and Introduction

Chapter three describes a study which investigated the quantitative effectiveness of a medicine authentication technology from a technical and operational point of view. Chapter three describes how this technology was piloted in a live hospital environment and provides a better understanding of the obstacles which face hospital pharmacy regarding FMD compliance. Chapter three also assessed the best point in the hospital dispensing process to authenticate medicines. This chapter takes a more qualitative approach to technology assessment and aims to identify expert user opinion on the aforementioned technology and how it might be improved for future use.

Despite the 2019 legislative technology compliance deadline for pharmacies, dispensing general practitioner practices and hospitals across Europe, there is little qualitative evidence to support this international technological approach to falsified drug detection in practice. If implemented incorrectly this international change has the potential to cause considerable upset for healthcare providers. This study aims to qualitatively evaluate and inform the optimisation of medicine authentication technology in secondary care.

Stakeholders from different sectors, such as hospital pharmacy, community pharmacy, wholesalers, and pharmaceutical companies in

each EU country have joined to form a National Medicines Verification Organisations (NMVO). Each NMVO will make decisions regarding authentication technology providers which may relate to functionality, speed of data response, usability and technology limitations. The study aims to identify the positives and negatives of the incoming technology and educate decision makers as to the potentially useful technological changes that could be adopted or mandated as part of the incumbent medicines authentication technology.

A group of ten secondary care healthcare professionals with experience in medicines authentication were surveyed. Participants were surveyed directly following the stage two study in chapter three, which lasted for eight weeks and was conducted in 2015. The Delphi method approach was used to carry out this survey. The Delphi method approach, originally used as a systematic forecasting tool (119-120), has been increasingly used to gain consensus expert opinion and aid decision making in a variety of research areas. Delphi methodology provides clearer outcomes and recommendations than traditional surveys often produce, achieved by collecting responses and summarising responses for reconsideration by participants until a consensus is achieved.

User feedback and opinion can be gathered using many different approaches which include, basic surveys, qualitative interviews or the Delphi method survey approach. The key to this stage of the study was to encourage users to identify technological improvements based on their recent use of the technology. It was considered important to allow the users a forum to freely express their thoughts without being judged by the

researcher or their peer group. At the same time, it was important for users to consider the opinions of their peers. The Delphi study allows for the contributions of opinions while removing the element of peer pressure and maintaining anonymity. This consensus approach is an effective way of involving users and making changes which support the views of the majority.

The planning of this study was based largely on the Hsu and Sandford paper (120) which describes evidence for successful Delphi studies such as the number of survey rounds, consensus figures and thematic analysis (120). Delphi method consensus varied across studies and opinions differ on a suitable percentage of consensus. This study compliments those conducted by Green in 1982 (24) and Ulschak in 1983 (25) (in Hsu and Sandford in 2007) (120) which promote a consensus of 70% and 80% respectively. The default consensus in this study was 70% with 80% used where possible. The standard deviation was chosen as a method to measure central tendencies with an arbitrary <1.0 SD used to supplement the consensus. This quantified the spread of responses across the entire group. The Delphi method generates useful improvements, suitable for the context in question and facilitating staff involvement in change (121).

4.2: Methods

Twelve participants from a UK hospital pharmacy department with experience of using medicines authentication technology as part of a service evaluation project and satisfied the study inclusion and exclusion criteria (**Table 4.0**) were invited to take part in a Delphi method study. An

implied consent model was used, with information regarding the nature of the study contained in the invitation email (119-120,122-124) and repeated on the first page of the questionnaire. This information described the study and its voluntary nature. From a total population size of 12, 11 invitations were accepted. One staff member was unavailable to attend the interview due to sickness, and one staff member was initially invited inappropriately, as they did not meet the inclusion criteria. 100% (n=10) of available eligible participants responded.

Table 4.0: Inclusion and exclusion criteria for study participants.

Inclusion criteria
Staff accredited in the professional checking process at the test site[1]. Staff with multiple experiences of using the authentication technology. Staff willing to complete multiple surveys. Staff that have attended basic training as part of the stage one project on medicines authentication (chapter three).
Exclusion criteria
Staff that have used the system once or not at all. Staff that has not passed the trust checking accreditation test.

Prospective participants were asked to complete an electronic questionnaire (119,125) with an estimated completion time of 15 minutes or less. Participants received a total of two questionnaires (123) (i.e. one

[1] Staff were a mixture of GPHC (General Pharmaceutical Council) registered pharmacists and GPHC registered accuracy checking technicians (nationally recognised qualification).

for each of the two rounds of the study). The initial invite was followed by reminders at approximately 8-day intervals until completion. The question and response format included three different categories of questions (**Table 4.1**), a 7-point rating scale, a Likert scale and a descriptive or open-ended response format. Likert scales were used to prioritise suggestions for the improvement of the technology made by participants during stage one (chapter three) and the first round of this Delphi study. In some cases, the staff identified four suggestions, and in some cases, they identified five suggestions, therefore two Likert scales were employed (1-4 and 1-5).

Table 4.1: Question Types

7-Point rating scale: This question format rates performance from 1 to 7, with '1' indicating a negative response and '7' indicating the most positive response. The median response was collected for consensus evaluation.
Likert scale response format: This question style requires respondents to prioritise suggested improvements, regarding importance from '1' to 4' or '1' to '5' with '1' indicating most important and '5' indicating least importance (median).
Descriptive or open-ended response format (d): This response format does not require prioritisation or rating, rather the suggestions are summarised into improvement ideas and resubmitted to the participants for consideration. In round two, participants were then asked to rank the importance of these suggestions in order of importance (Likert scale).

4.2.1: Consensus

The 7-point rating scale consensus was achieved when 70% of respondents selected either of two adjacent answers on a seven-point rating scale (i.e. 1 or 2, 2 or 3, 3 or 4 etc. (126) and the median score fell within the range of the two consensus answers (127) (**Table 4.2**). Regarding the 5 point, Likert scale question format (126) consensus was achieved when 80% of the respondents selected one of three adjacent

answers in either direction i.e. whether participants classed the suggestion as “important” (1-3) or “not important” (3-5). The same rules were applied to the 4-point Likert scale. However, ‘Important’ was classified as 1-2 and ‘not important' was classified as 2-4, with the consensus achieved when 70% of respondents selected one of two answers in either direction (i.e. 1 to 2 or 2 to 4) (**Table 4.2**). In the case of a 5-point scale, the median must also have been below 2.5, and in consideration of a 4-point scale, the median score must also have been below 2 to be considered ‘important’ (120) (**Table 3.0**).

Regarding the Likert scale questions generated from the descriptive or open-ended questions in round one. Consensus was assessed dependent on the theme of the response, e.g. if 80% of respondents selected one of three descriptive adjacent answers of the same sentiment (positive or negative) on a 5-point scale and the median score fell within the consensus category.

Table 4.2: Summary of consensus.

Question Type	Consensus (%)	Median response	Consensus Description
7-Point Rating Scale	70% agreement	Must fall within the consensus category	One of two adjacent answers
Likert Scale 5 point	80% agreement	<2.5 (Important)	One of three adjacent answers in either direction
Likert Scale 4 point	70% agreement	<2 (Important)	One of three adjacent answers in either direction
Descriptive/Open	Used only in round one. Suggestions were grouped into similar themes and participants in round two were asked to rank them according to importance (Likert scale)		

4.2.2: Summary of Survey Rounds

Round one involved three demographic questions, followed by a selection of closed questions relating to rating scales, performance and open questions requiring suggestions for technological improvements. These questions were followed by descriptive questions to evaluate the quality of the survey. A selection of questions was chosen based upon written feedback from users, during a stage one of the study which involved the use of authentication technology during an eight-week period. Round two was similar to round one. However, closed questions that achieved consensus were removed. Non-consensus questions were re-submitted to the participants with further explanation.

Answers to the open-ended questions in round one were thematically categorised and summarised to remove duplicate suggestions. In round two the experts were asked to answer further questions based on the most frequently occurring themes, which included Likert scales or descriptive style questions. The total number of suggestions per question varied between four and five suggestions which directly affected the number of options available in the round two survey. A valid consensus result was considered as 'achieved' when consensus had been met and the median scores also fell within the consensus group (**Table 4.2**). Suggestions that fell within these parameters and had a standard deviation of less than 1.0 were considered as the most relevant improvements for the authentication technology. There was no follow up with participants after study completion.

4.2.3: Ethical Approvals

This study was classified as a service evaluation project according to NIHR guidelines and PhD supervisors and therefore did not require ethical approval.

4.3: Results

The questions which reached immediate consensus are described in **Table 4.3** and **Table 4.4**. Answers in text boxes with no shading identify the results which reached consensus with a low standard deviation less than one (<1.0). Answers in text boxes with grey trellis shading identify a consensus response with a standard deviation of greater than one (>1.0). Standard deviation (SD) was not used to determine consensus. SD was used as a further measure, to identify consensus results with the smallest deviation from the group mean.

Table 4.3: A summary of 7-point rating scale results

No	Question	Result (Median)	Std. Dev. (SD)
4	Based on your experience of the Medicines Authentication System (MAS), how would you rate its general speed on a scale of 1 to 7? (1 represents very slow, and 7 represents very fast)	6/7	0.75
5	Based on your experience of the MAS, how would you describe its usability on a scale of 1 to 7? (1 represents very difficult, and 7 represents very easy)	6.5/7	0.87

6	There were some system errors reported by the MAS users throughout the pilot. On a scale of 1 to 7, how often did you experience these types of errors? (1 represents never, and 7 represents very often) (These errors may have included issues with reading the 2D barcode, duplication of the scan on screen or warnings such as "The system has no resources",” item can is invalid please scan product again" or "test product not found")	1/7	0.67
Round 2			
7.	Question 4: How would you rate the impact of the MAS on the service you provide on a scale of 1-7 (where 1 represents very disruptive, and 7 represents very helpful)?	4/7 (Not disruptive)	0.94

Table 4.4: A summary of 4 and 5-point Likert like scale results.

No	Question	Result (Median)	Std. Dev. (SD)
Round 1			
7	The following are a list of reported, proposed improvements. Please rank them in order of importance (1-5)		
7(ii)	Change the medicine scanning list on the screen to ensure the last scanned item appears on the top of the list	1 (Important)	SD 1.25
7(iv)	Review the pop-up screens as the Red ‘warning’ screens could be mistaken for the common “already dispensed here’ screen.	2 (Important	SD 0.87
7 (v)	Incorporate ‘important information’ pop-ups into the authentication system	2.5 (Important)	SD 1.25
Round 2			
5	During round one of this survey, further suggestions were made to improve the Medicines Authentication System (MAS) or the pilot. Please rank the suggested changes below in the order of importance (1 being most important and 5 being least important).		
(ii)	Sounds could also be enabled to ensure warnings/information are noticed (MAS)	2.5 (Important)	SD 1.2

6	During round one of this survey, there were a variety of suggestions made to increase the rate of authentication (scanning). Valid suggestions were subdivided into three categories 1. Process Change 2. Technology change and 3. Education. In terms of Process Change, please rank these suggestions in order of importance (with 1 being the most important and 5 being the least important)		
(I)	Make the symbol indicating an item that needs to be scanned larger/more visible (Process)	2.5 (Important)	SD 0.92
7	During round one of this survey, there were a variety of suggestions made to increase the rate of authentication (scanning). Valid suggestions were subdivided into three categories 1. Process Change, 2. Education, and 3. Technology change in terms of Education and Technology change please rank these suggestions in order of importance (with 1 being the most important and 5 being the least important)		
(iv)	A system change that knows how many items have been booked in and prescription is not able to be tracked out as verified until all medications have been authenticated (Technology Change)	2.5 (Important)	SD 1.2
8	During round one we explained that there had been occasions where products have been handed out despite showing a pop-up warning box. We asked you to list three suggestions of how this occurrence might be reduced. Valid suggestions were subdivided into two categories 1. Education and 2. Technology change. In terms of education please rank these suggestions in order of importance (with 1 being the most important, and 4 being the least important)		
(I)	Encourage the dispenser or checker to take action on the warnings (Education)	2.0 (Important)	SD 1.0
9	During round one we explained that there have been occasions where products have been handed out despite showing a pop-up warning Box. We asked you to list three suggestions of how this occurrence might be reduced. Valid suggestions were subdivided into two categories 1. Education and 2.		

	Technology change. In terms of technology change please rank these suggestions in order of importance (with 1 being the most important and 4 being the least important)		
(ii)	An audible alert to accompany the pop-up warning box (Technology)	1.00 (Important)	SD 0.9
(iii)	Making it mandatory to complete an 'action taken' documentation process so that staff scanning are prompted to think about what the red warning means and be accountable for it (Technology)	2.00 (Important)	SD 0.94

The most important suggestions in this study are those which established consensus amongst the group (**Table 4.3 and Table 4.4**) with a narrow standard deviation. Improvements included reviewing the colour and information in warning pop up screens to ensure they were not mistaken for the "already dispensed here" pop up (2.0)(SD 0.87), encouraging the dispenser or checker to act on the warnings (2.0) (SD 1.0) (Education), including an audible alert to accompany the pop-up warning box (1.0) (SD 0.9) (Technology), and making it mandatory to complete an 'action taken' documentation process to improve the quarantine process for potentially counterfeit, expired or recalled medicines. (Technology) (2.0) (SD 0.94). A full list of questions and results can be found in **Appendix 4.0.**

4.4: Discussions and Conclusions

The serialisation and authentication of medicines have been proposed as part of international regulation. Considering that serialisation and verification with or without authentication will affect EU hospital pharmacies and is likely to affect US hospitals wishing to wholesale

supply, it is important to gauge its current appropriateness and identify improvements for this technology.

There were no concerns regarding the speed and usability of authentication technology raised during this chapter. There was limited impact on the daily activity of the staff and was classed as 'not disruptive'. This study also identified some suggestions to improve authentication and detection rates including the importance of making a clear differentiation between the various warning messaging to avoid misinterpretation. Participants identified a concern with the similarity of warning messaging which may have had an impact on the decision to quarantine and may have contributed to the suboptimal detection rates seen in chapter three relating to the chapter three. Phansalkar et al. (128) explained that colour plays an important role in the differentiation between alerts on clinical information systems. As seen in this technology, Phansalker explains that red, amber and green are commonly used colours to differentiate between alerts. Phansalker states that

> '*Color, shape, and size are the variables commonly manipulated to make visual alerts distinct from one another, although these manipulations must take into account any coding for prioritisation'*.

In the technology investigated in this chapter and in chapter three the same colour (amber) with a different written message, was used to identify two alerts which required two different actions (128). The participants in this study made a suggestion which supports Phansalkers point. The participants suggested that the colour of the amber alerts which required

quarantine should be changed to red to help them to prioritise the action that should be taken.

As with all changes to practice, adequate education and training are required. There was a basic presentation and education approach used which included the provision of an authentication protocol used in the previous chapter (**Appendix 2.0**). This may have contributed to inadequate authentication and detection rates due to the use of standard educational support or perhaps due to the sheer volume of procedures and protocols that staff are required to adhere to as part of the normal working day. The systematic authentication of medicines is a big change of practice and may benefit from a structured training and revalidation package. If we refer to previous large information technology projects such as the implementation of the electronic patient record (EPR). This was a much more complicated electronic system with a structured training package which largely includes presentations, demonstrations, workshops, drop-in sessions and protocols. A varied, informed and interactive approach, as used in the EPR project, is required to build operator background knowledge and to instil the clinical and legal importance of authenticating medicines as well as the impact of authentication on medicine detection rates.

The quantitative service evaluation study in chapter three identified a disparity between medicines identified as requiring quarantine and those actually quarantined. This qualitative study contained within this chapter demonstrated a consensus that a pop-up warning message alone is not an adequate prompt in the complex, non-linear and busy

hospital environment. The operators in this study are in agreement that an extra noise to indicate that a medicine requiring quarantine would improve the effectiveness of this technology. Not only would this remind the operator to act but it may also bring attention to the entire team that a medicine requiring quarantine had been identified, generating peer pressure to act on the warning.

Participants also emphasised the importance of an electronic 'action taken' documentation process. Operators relied on recording the medicine for quarantine on a paper proforma sheet located beside the terminal; their view was that this could be improved with the inclusion of an 'action taken' function incorporated into the authentication technology software. In a systematic review study by Shojania et al. the action taken alert has been identified as potentially more effective than a 'non-action' alert, (11) demonstrated in a small group. This 'action taken' approach may facilitate an improved detection rate and may also support a reporting system which would benefit managerial monitoring of falsified, recalled or expired medicines within a department. This would also allow staff responsible for product quarantine to tally medicines physically quarantined with medicines identified by the technology as requiring quarantine.

Information technology systems such as electronic prescribing, or in this case medicines authentication technologies are relatively new approaches to optimise healthcare information. Shojania et al (118) demonstrate that evidence to support computer alerts is currently limited. Regarding electronic prescribing, Shojania concludes by stating 'Further

research must identify design features and contextual factors consistently associated with larger improvements in provider behaviour if computer reminders are to succeed on more than a trial and error basis'. Further research is also required regarding medicines authentication technology to identify the approaches which facilitate operational compliance. Hospitals in the NHS vary slightly depending on the services they provide, which makes context an important factor in technology success (98). Following on from the remarks made by Shojania et al. further research is required to understand how contextual factors can facilitate successful technological projects in the UK National Health Service. One such contextual factor may include incentives to authenticate medicines. The use of reimbursement codes within the 2D data matrix is hypothesised to help the authentication rate of medicines, a practice seen in the Belgian community pharmacy setting. There will be a legal mandate to authenticate medicines. However, incentives such as reimbursement upon authentication may prove to augment authentication and detection rates.

The results of this study should inform key opinion leaders, policymakers and technology manufacturers regarding medicines authentication technology and potential authentication technology improvements. Considering the limited evidence to support medicines authentication the outcomes of this study should also service decision makers in their discussions surrounding the selection of medicines authentication technology providers. Considering the suggestions identified in this chapter, chapter five aims to implement an active sound

alert and re-assess the digital MAT approach to understand the effect of an 'Active' audio alert on digital drug screening.

Note: The majority of this chapter was published in the following publication.

Naughton B, Roberts L, Dopson S, Brindley D, Chapman S. Medicine authentication technology as a counterfeit medicine-detection tool: a Delphi method study to establish an expert opinion on manual medicine authentication technology in secondary care. BMJ Open. 2017 May 6;7(5):e013838.

5.0: The Effect of a User Instigated Audio Alert on the Authentication and Detection Rate of Falsified, Expired and Recalled Medicines in the Hospital Sector

5.1: Introduction

Chapter three discussed the effectiveness of medicines authentication technology at the end of the supply chain, in a hospital setting (73) and chapter four discussed improvements to this technology. As explained previously medicines authentication technology involved the scanning of a two-dimensional barcode and digital crosschecking against a national database to determine whether or not a medicine had been recalled, expired or potentially falsified. The technology example employed, coloured pop-up alerts to identify a medicine as requiring attention (amber) or quarantine (red) or no action (no pop-up, a purple symbol to acknowledge the scan had been completed successfully). Chapter three identified a number of issues related to the relatively poor authentication and detection rate of this approach. Accuracy checking technicians and pharmacists at the checking stage of medicine supply were identified as the best-placed personnel within the dispensary to carry out the decommissioning process, based on scanning compliance data. The authentication technology in chapter three didn't experience any technical communication issues (with the exception of occasional offline episodes) and had a favourable average response time of less than 300 ms. However, not all medicines in the chapter three study were scanned and of those scanned not all were appropriately quarantined according to the study

protocol (**Appendix 2.0**) This demonstrated a significant operational quality concern with the digital medicine screening approach (73).

Pop-up alerts have been used by many health information technologies (HIT'S) over the years to alert healthcare professionals to important information such as prescribing reminders or counselling advice. There is, a scarcity of research related to the effectiveness of these pop-up alerts in health information technology; the research that does exist relates to the point of care computer reminders, associated with electronic health records and medical prescribing systems. A systematic Cochrane review by Shojania et al. in 2010 (118) investigated the effect of point-of-care computer reminders on physician behaviour and identified that computer reminders improved the process of care by a median of 4.2%. As mentioned in previous chapters, this improvement was smaller than what was expected from the implementation of computerised order entry and electronic medical record systems. In chapter four it was explained that Shojania et. al. introduced the concept that reminders may not be as effective as first anticipated and that 'active' reminders may be of most benefit, although this was based on limited data.

This chapter aims to repeat the chapter three study under nearly identical conditions with one alteration to the Medicines Authentication Technology (MAT). This change involved the inclusion of an audio alert, which was suggested by study participants as part of the Delphi method study (129) discussed in chapter four. This audio alert, sounded upon the authentication of a falsified medicine (authenticated elsewhere), authenticated here medicine, expired pack, recalled pack, or recalled

product. The primary aim was to understand if the audio alteration would affect the detection rate of expired, recalled and potentially falsified medicines.

5.2: Methods

5.2.1: Objectives

Primary Objective

- To identify the OAR, ODR and ADR rates of falsified, recalled or expired medicines over an eight-week period using a MAT with a sound alert and to compare this to the identical scenario without a sound alert from chapter three.

Secondary Objectives

- To establish MAT offline frequency (how often the system failed to connect to the database).
- To identify the frequency of false positives in this approach.
- To identify MAT response times (how long it took for the technology to communicate with the database and return a response).

5.2.2: Study Site

This study was performed in the same NHS teaching hospital trust site which hosted the baseline study in chapter three.

5.2.3: Technology Alteration

A MAT was altered to generate a sine waveform, with a frequency of 530 hertz and sound length of 1 second. The volume was between 90 and 98 decibels.

5.2.4: Product Serialisation Method

The sample used from chapter three was replicated for this chapter. Medicines were labelled with a pre-programmed two-dimensional barcode sticker, twice a week, every week in the morning and early

afternoon for an eight-week period to ensure that product lines in the study remained serialised for the entire eight weeks as per chapter three. The pre-programmed 2D barcode sticker identified each product as being 'authenticated', 'already authenticated here', 'authenticated elsewhere (falsified)', 'product recalled', 'batch recalled' or 'expired' at frequencies described in **Table 5.0.** The results from chapter three acted as the control with the new data contained within this chapter acting as the intervention. For ease of reference and comparison, the results from chapter three are represented in this chapter also. Medicines with serialised stickers attached were recorded in a database controlled by the researcher; this was compared to the medicines quarantined by the staff members and those recorded as scanned by the MAT provider's database. Data analysis was conducted by two separate researchers to ensure the analysis was accurate.

Table 5.0: A description of each pop-up alert and corresponding frequency throughout the investigated sample.

Popup Message (Colour)	Frequency as a percentage of serialised products entered into the study
Authenticated (Passive purple symbol)	96%
Already Authenticated here (Amber)	Naturally occurring
Authenticated Elsewhere/Falsified (Amber)	1%
Product Recalled (Red)	1%
Pack Recalled (Red)	1%
Pack Expired (Red)	1%

5.2.5: Statistics

Percentages have been used for normalisation. To demonstrate a significant difference between the outcomes in this chapter and chapter three, Chi-squared tests and Fisher's exact tests have been used. Both tests

are suitable for nominal data however Chi-squared test is suitable for sample sizes greater than 1000 and the fishers exact test is best suited to smaller sample sizes. A p value of <0.05 is deemed as being statistically significant, and confidence intervals of 90% have been used throughout (109, 130-133)

5.2.6: Comparability of Studies

The method used in this study was almost identical to the approach taken in chapter three, stage one (Medicine decommissioning by pharmacists and accuracy checking technicians at the checking stage). The same portfolio of medicines was used over an eight-week period and the participants were given the same presentation and demonstration of the authentication technology as per the protocol. Despite the best efforts of the researchers, there may have been some perceived differences between both studies, these are noted in **Table 5.1.**

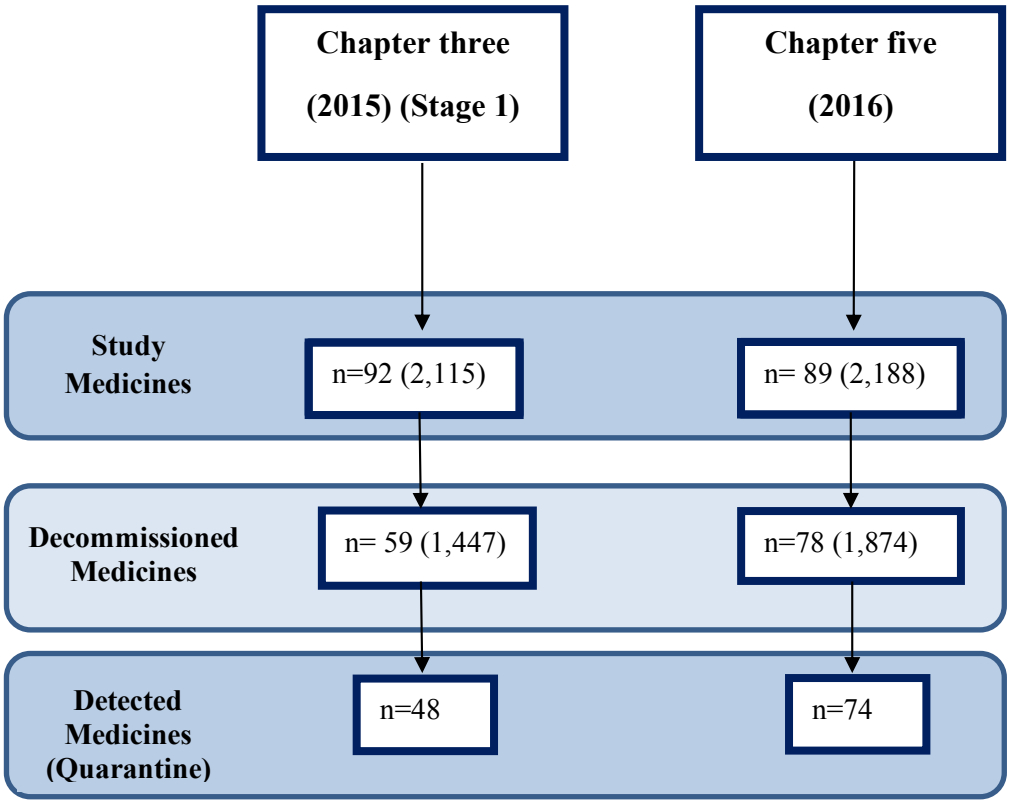
5.2.7: Ethical Approvals

This study was classified as research according to NIHR guideline's and as such required ethical approvals which can be found in Appendix 4.0, p 290. HRA approval and Trust R&D approvals were also required which can also be found in Appendix 4.0 (p293 and p294).

Table 5.1: Potential differences between the 2015 study (chapter three) and 2016 (chapter five).

Chapter Three (Stage one)	Chapter Five	Considerations
No previous exposure to medicines authentication technology	Previous exposure to medicines authentication technology	Previous results have not identified an association between exposure and increased compliance. There was a greater than one-year interval between studies
Conducted as a service evaluation study	Conducted as a research study	The chapter five study involved ethical approval and written consent
This study was proposed by the researcher	The study was based on a consensus improvement suggested by the participants	Compliance may have been increased by the motivation to implement an idea that was suggested by the participants

5.3: Results



Key

n= Number of study products containing error messages.

(...)= Number of total serialised products entered into the study.

Figure 5.0: A flow chart which identified the total number of medicines included in both studies (study medicines), the total number of medicines scanned (decommissioned medicines) and the total number of medicines detected (detected or quarantined medicines).(73)

This chapter and chapter three refer to studies carried out in 2015 and 2016 respectively and were each conducted over the same duration, using the same 30 serialised medicines, which explains the similar number of products serialised in each study. **Figure 5.0** shows the number of medicines authenticated was greater in the 2016 study; this higher authentication rate correlates to the higher number of medicines detected

by the authentication technology and therefore the higher rate of medicine correctly quarantined by the operator in response to the technology alert.

Table 5.2: A demonstration of the OAR, ODR and ADR during the 2015 and 2016 studies.

Parameter	Chapter Three (2015)	Chapter Five (2016)	Difference
Operational Authentication Rate (OAR)	68% (66.8-70.1%)	85.6% (84.4-86.9%)	+17.2% (15.2-19.3%) p<0.05 (Chi squared test) (109)
Operational Detection Rate (ODR)	81.36% (73-89.7)	95% (90.8-99.0)	+13.5 % (4.21-22.81%) p<0.01 (Fishers Exact Test) (109) (111)
Absolute Detection Rate (ADR)	52.2 % (43.6-60.7%)	83% (76.6-89.7%)	+30.1% (20.2-41.7%) (109) (111) p<0.05 (Fishers Exact Test) (109)
90% confidence intervals used throughout (108, 110).			

There has been a statistically significant improvement in authentication and detection rates in the 2016 study compared to the 2015 study. During the 2016 study, regular evaluations of the technology were performed to ensure the technology was accurately communicating with the external database. And no issues were identified in this regard. There did appear to have been instances where the medicine authentication technology identified a medicine as requiring quarantine, and staff failed to do so which is represented by an ODR of less than 100% **(Table 5.2).** MAT communication with the database was assessed to understand the

factors contributing to poor quarantine compliance. In all cases of instruction to quarantine by the MAT, without appropriate quarantining, there were no offline issues at the time of notification. The technology records data in coordinated universal time (UTC) and from the seven cases in the 2016 study where medicines were authenticated but not quarantined; there was no trend which indicated the type of medicines day or time of day as a factor which contributed to quarantine non-compliance. The same examination took place for medicines with alerts which were included in the study but not scanned (12) and again there was no clear indication that the medicine type affected authentication compliance.

Table 5.3: A breakdown of study medicines with alerts, medicines authenticated, and medicines detected during the 2015 (chapter three) and 2016 (chapter five) studies.

Year	Authenticated elsewhere (falsified)	Product recalled	Pack recalled	Pack expired
	Study medicines with alerts			
2015	22	24	24	22
2016	21	23	22	23
	Decommissioned medicines			
2015	13	12	18	16
2016	16	22	20	20
	Detected medicines (quarantine)			
2015	7	12	13	16
2016	12	22	20 (21[2])	19

[2] There was one case where the medicine was quarantined without being scanned. Upon investigation, it appears that at the time of quarantine the technology appeared to be offline. This resulted in a number of medicines being quarantined on precaution. All but one, were initially authenticated.

The data in **Figure 5.0** describes medicines serialised and the proportion of which contained error alert stickers. **Table 5.3** breaks the total number of serialised medicines with alerts down to the individual alert categories i.e. 'authenticated elsewhere' (falsified), 'product recalled', 'pack recalled' and 'pack expired'. Through breaking down the group of serialised medicines with alerts into each of the four component groups, we can compare inter and intra-group detection rates. It is clear that the 'authenticated elsewhere' or potentially falsified alert generated a lower number of appropriately quarantined outcomes.

Table 5.4: Operational detection rates (ODR) for each alert group.

Alert	**2015**	**2016**	**Difference**	**Stats (Fishers exact test)**
Authenticated elsewhere (Falsified)(Amber)	53.9% (31.1-76.6%)	75.0% (57.2, 92.8%)	21.2% (-7.73-50.0%)	p=0.16
Product recalled (Red)	100.0% (100-100%)	100.0% (100,100%)	0.0% (0,0%)	p= 1.0
Pack recalled (Red)	72.2% (54.9-89.6)	100% (100.0, 100.0%)	33% (10.4-45.1%)	p=0.017
Pack expired (Red)	100% (100.0-100.0)	95% (87.6-102.9%)	5% (12.4-2.9%)	p=0.58
90% confidence intervals used throughout (108, 110)				

The ODR in all alert groups (**Table 5.4)** (calculated from data in **Table 5.3**) demonstrates either no improvement or modest improvements in operational detection rates across all groups between 2015 and 2016.

This change is not statistically significant in most cases which is likely due to small sample sizes in each group.

Table 5.5: Absolute detection rates (ADR) (the ratios of medicines correctly quarantined by the operators as a proportion of those entered into the study) for each alert group.

Alert	2015 Study	2016 Study	Difference Stats	Stats (Fishers Exact Test)
Authenticated Elsewhere (Falsified)	31.8% (15.5-48.2)	57.1% (39.4-74.9)	25.3% (1.19-49.46)	p= 0.06
Product Recalled	50% (33.2-66.8)	96% (88.7-102.6)	46% (27.5-63.8)	p<0.05
Pack recalled	54.2% (37.4-70.9)	91% (80.8-101)	36.7% (17.2-56.3)	p<0.05
Pack expired	73% (57.1-88.3)	83% (69.6-95.6)	10% (-10.4-30.2)	p=0.21
90% confidence intervals used throughout (108, 110)				

The ADR, is an especially important statistic from a patient safety perspective, as it identifies the number of falsified, expired and recalled medicines detected as a percentage of the total number of medicines dispensed. The ADR improved between the 2015 and 2016 study across all alert groups. The group with the lowest ADR is the falsified medicine group, with all other groups demonstrating improvements, moving close to acceptable standards (close to 100%). Chapter three identified that there were two amber pop-up alerts one which required quarantine (Authenticated elsewhere or falsified) and one which did not require quarantine (Authenticated here) (**Table 5.0**). The 'Authenticated elsewhere or falsified' alert was commonly mistaken and resulted in the lowest ADR.

Table 5.6: The ADR in the falsified group (amber) versus other groups combined (red) (expired and recalled)

ADR	Falsified alert group (Amber)	Other alert groups combined (Red)	Difference
2015	31.8% (15.5, 48.2)	58.6.1% (48.9, 68.3)	+26.8% (7.8, 45.7%) P<0.05
2016	57.1% (39.4, 74.9)	88.2% (81.8, 94.7)	+31.1% (12.2-49.98) p<0.05
90% confidence intervals used throughout (108,110)			

Table 5.7: The ODR for the falsified group (amber) versus all other groups (expired and recalled) (red).

ODR	2015 & 2016 Combined	Difference	Statistics (Fishers Exact Test)
Falsified Alert group (Amber)	65.5% (51.0-80.0)	29% (14-43.9)	p<0.0001
Others Alert Groups Combined (Red)	94.4% (90.8-98.1)		
90% confidence intervals have been used throughout (108, 110)			

Table 5.6 shows a similarity in the disparity between the falsified group and all other alert groups across both studies. Despite the 2016 study showing improved results all round, there is still a similar difference between the ADR of medicines which contain a red alert (all other groups) and an amber alert (Authenticated elsewhere, potentially falsified). When comparing the cumulative data from 2015 and 2016 it is clear that the detection rate of 'Authenticated elsewhere' (falsified) shows worse outcomes than all other alert groups combined **(Table 5.7)**.

Table 5.8: The response times frequencies of offline issues in the chapter three and five studies.

Parameter	2015 Study	2016 Study	Expected Standard
MAT response times	152 ms (n=1604)	131ms (n=2503)	300 ms
MAT Offline frequency	0.44% (n=1604)	4.67% (n=2503)	Undefined

The EU FMD has mandated a maximum data round-trip (from scanning to external database and back) response rate of less than 300 milliseconds. Across both studies, this has been achieved with a faster response rate observed in the 2016 study. Offline issues, however, appear to have been more frequent in the 2016 study with >4% increase when compared to the 2015 study results. False positives were recorded in both studies. A false positive refers to when a medicine is identified as requiring quarantine when in fact it does not require quarantine, also known as a false alarm. There were 11 cases in 2015, three of which were related to offline issues and 37 cases in 2016, of which 17 were related to an offline issue. The false positive figure for the 2015 study was extracted from previously gathered data.

False Positives and False Negatives

Table 5.9: False positives.(110, 134)

	2015	2016
False positives	11 (of which three were related to an offline issue)	37 (of which 17 were related to an offline issue)

The basis of a good diagnostic test relies on its sensitivity and specificity. Sensitivity, detection, or true positive rate measures the proportion of positives identified as such by the test. Specificity or true

negatives, report the proportion of negatives that are correctly identified by the test. This technology was tested by the company providing the solution and the researcher also performed ad-hoc testing throughout the studies to ensure than medicines with preprogramed alerts were being identified to the staff and therefore the technical sensitivity and specificity was accepted as 1.0, as long as the technology was online. This approach is not entirely technical and relies on the interpretation of alerts from the user in a busy environment and the patience to deal with offline issues. **Table 5.9** identified that the incidence of false positives in 2015 was less than 2016. This correlation may be due to the increased instances of offline issues identified in **Table 5.8.**

Workarounds

Finally, it was observed during this study that workarounds were created by the staff. During instances where medicine would not scan, due to an offline issue or otherwise, staff tended to quarantine the product as a matter of course. It was also observed that after the staff had authenticated a product that was only partly used they would use a pen to place a cross through the 2D data matrix to identify the part pack medicine as already having been authenticated.

Discussion

To knowingly introduce expired, recalled or potentially falsified medicine into the legitimate pharmaceutical supply chain would be disruptive, unethical and compromise patient safety. The 2015 and 2016 studies safely assessed the authentication rate, detection rate, response time, false positive frequency and offline frequency in a controlled, live,

closed-loop environment without compromising patient safety. Post FMD implementation, it may be possible to investigate the prevalence of expired, recalled and counterfeit medicines, this has been done in part in studies in Belgium where the authentication of medicines is commonplace (104). However, medicine scanning or authentication is only effective if all medicines are scanned. It will not be possible to identify the absolute detection rate of expired, recalled or counterfeit medicines in the supply chain unless the total number of falsified medicines in the legitimate supply chain are known from the outset, and all products are scanned. Therefore, this study is uniquely positioned.

False Positives and Response Times

The 2015 study identifies an increase in false positives between 2015 and 2016 **(Table 5.9)**. The MAT was accuracy tested before use in the chapter three and five studies. The ad hoc testing performed by the researcher aimed to identify instances of false negatives throughout the studies to ensure than medicines with preprogramed alerts were being identified to the staff as such. The researcher did not experience any false negatives during testing, however there may have been cases where the technology gave no result e.g. during offline periods. However, it was not possible to quantify the incidence of this occurrence. The number of medicines quarantined that did not require quarantine (false positives) were compared with the offline issues. It is theorised that the increase in offline issues **(Table 5.8)** caused confusion regarding the test result. This confusion resulted in the inappropriate quarantine of products. The impact of offline instances (when the scan from the terminal cannot communicate

with the national database) on healthcare institutions will cause a delay in the supply of medicines to patients, this study suggests that an increase in offline issues will result in an increase in false positives. There is no evidence in this study to suggest a relationship between false negatives and offline issues. An option permitted by the FMD during the offline technology scenario is to supply a medicine without evaluating the provenance of the product or halting medicine supply until the system is back online. Supply without authentication is a risky strategy from a professional litigation perspective, and it is not yet understood what would happen in the instance where the technology failed and remained offline for a period of time, resulting in a dangerous medicine being dispensed without first being authenticated. Although this technological approach has proven its ability to operate at speeds well below the FMD mandated limit of 300 milliseconds, it is clear from this study that offline issues have an effect on false positives and are likely to disrupt the delivery of medicines to patients. One way to keep offline issues to a minimum would be to penalise the NMVS provider for offline instances beyond an agreed contracted level.

The Impact of an Audio Alert on Adherence to Policy

It is anticipated that the inclusion of an audio alert, as suggested by participants would improve the operational detection rate of medicines at the point of decommissioning, in an otherwise audio alert naïve environment. The outcome of the 2016 study, when compared to the 2015 study, was favourable in terms of all key measures, operational authentication rate, operational detection rate, and absolute detection rate.

As there was only one major change from the 2015 study, it would be reasonable to attribute these changes to the inclusion of an audio alert. Other factors may have also played a role in the improvement in the decommissioning and detection rate, and these are explored through qualitative interviews in chapter six.

Shojania et al. explained that the use of computer reminders improved adherence to process of care by a median of 4.2% over 28 trials which was described by the authors as being 'much smaller than those expected by electronic health records'(135). Although information pop-ups alone have shown limited effectiveness in the medical record and prescribing environment there is a sample of data which identifies that reminders which require the user to enter a response generated a 12.9% median increase. The 12.9% increase parallels with the active sound alert used in this chapter which improved the ODR by 13.5% between chapter three (2015) and chapter five (2016) (**Table 5.2).** This phenomenon can be seen across all medicine pop up groups as well as each individual pop up **(Table 5.5).**

The healthcare environment can at times be chaotic and computer reminders or pop-ups can be ignored as frequently as 49% to 96% of the time as described by Van der Sijs et al. (135). It is worth considering whether or not an 'active' computer alert, such as a visual alert which requires the user to enter a response, or something as simple as a specific noise alert may be more beneficial than a passive computer reminder. A passive computer alert may result in staff skipping through pop-up alerts or using a workaround to bypass perceived unnecessary interruptions to

deal with direct patient care. Considering this theory, it is also important to consider the contextual factors which may affect new computer alerts. The pharmacy environment in the UK and many other European countries use electronic patient medication records which employ a variety of medication and patient safety alerts. These alerts have the potential to condition healthcare staff to ignore pop-up alerts as seen in studies by Indermitte et al. in 2007 (136) where the overriding of computer alerts is community pharmacy has become commonplace. The results from this thesis showed that the rate of overriding contrasted to Van der Sijs 2006 study (135). The results in this thesis demonstrated an operational detection rate of 83.36 % (Chapter three) and 95% (Chapter five) which meant that 16.64% (Chapter three) and 5% (Chapter five) of the pop-up alerts were not acted upon. The improvement is likely due to the addition of the 'active alert' however other factors may also have influenced this outcome.

Peer Pressure and 'The Hawthorne Effect'

During the 2016 study, the addition of a simple audio alert brought about a change in operational detection, at the point of scanning this resulted in a difference of 13.5% between studies. This result may have been wholly or partially the result of an 'active alert' however the 'Hawthorne effect" associated with the audio alert may also have influenced this improvement and reduced the risk of pop-up blindness. The Hawthorne effect is a type of reactivity in which the operator alters their behaviour in response to being observed. This is usually an unhelpful effect as the results recorded during the observation do not ordinarily

represent the day to day situation. The participants were not monitored by the researcher during the studies. However, there was always another employee working alongside each operator. The Hawthorne effect is usually related to people being observed by a researcher or manager. In this case, the effect is possibly present on more of a peer-to-peer basis. The Hawthorne effect or peer pressure may have brought about positive change in this study in two ways. Firstly, the audio alert made it very difficult for the technology operator to ignore the computer pop-up alert as it was accompanied by a sound alert which could be heard by anyone in the dispensary. This made it very difficult to ignore, either intentionally or unintentionally. Furthermore, it would be easy to close a silent pop-up alert on a computer terminal without being noticed by another colleague however an audio alert brings with it a peer expectation to act. Finally, the audio alert informed staff in the department that a team-mate had scanned a medicine which required action, this provided the on looking team-mate with an opportunity to help the operator deal with the alert. To credibly explore whether or not the Hawthorne effect had a more pronounced impact during the 2016 further qualitative interviews which are explored in chapter six were required.

Staff Engagement

A key finding from the systematic Cochrane review conducted by Shojania et al. (118) was that a well-developed home-grown clinical information system demonstrated a larger improvement when compared to other studies 16.8% vs 3.0% median p=0.04. It is interesting to understand why a home-grown technology would demonstrate such

improved adherence to the process of care. One theory may be that a home-grown technology lends its self to technological adjustments suggested by the staff members which results in the development of a solution which is contextually appropriate. Another theory is that a home-grown technology empowers the employees, which in turn drives compliance irrespective of the technological change. In the field of lean processes, the Toyota model is often referred to. Within Toyota, there exists a process called Jidoka which essentially means building in quality. Furthermore, Toyota also uses a process called process call JKK (Jikotei Kanketsu) which means building in quality with ownership or taking pride in your work. If a healthcare organisation has the flexibility to develop their own solution, tailored to their own needs with staff identified improvements like those demonstrated in JKK, it is theorised that this will improve overall compliance not only within the micro-process, in this case decommissioning medicine, but beyond the specific improvement to other related processes. This study covered the addition of a noise alert to identify when a medicine required quarantine; this improvement was a direct result of user consensus via a Delphi method study (129). Although it was expected that this audio alert would only affect behaviour at the point of scanning a medicine which required quarantine, the audio alert also increased compliance across the entire process. It was identified that the operational authentication rate improved from 68% (66.8-70.1%, 90% CI) to 85.6% (84.4-86.9%, 90% CI) which then had a knock-on effect to absolute detection rate, an improvement from 52% (43.6-60.7%, 90% CI) to 83% (76.6-89.7%, 90% CI). It could

be theorised that from Shojania et al., and the results from this chapter that the JKK principles of building in quality with ownership increased compliance beyond the micro process (to quarantine in the response to an alert) through into surrounding processes associated with the technology, in this case, medication authentication or decommissioning compliance (OAR). This concept is further investigated through operator qualitative interviews in the following chapter.

The Impact of Alert Colour on Decision Making

The explanation for the poor detection rate in the 'authenticated elsewhere' alert group (**Table 5.4 – 5.7**) relates to the amber pop-up alert which is very similar to the 'Already authenticated here' pop up which was also amber, the former required quarantine and the later did not. It is hypothesised that staff may have glimpsed at pop-ups and made rapid decisions based on colour and not the message content. It is expected that the staff mixed up the pop-up alerts due to similarity and therefore failed to quarantine correctly the potentially counterfeit medicines, a theory which is substantiated through the qualitative staff interviews which follow.

5.4: Conclusions

An audio intervention increases the operational detection rate of medicines. Compliance with the technology as a whole has increased between chapters three and five which is a likely effect of the JKK theory or building in quality with ownership by involving staff in the interventional change. Similarities in pop-up colour alerts were also

observed as causing staff confusion and, in this case, have resulted in poor ODR of the falsified medicine group. Response times below 300 ms are realistic and have been proven possible over both the 2015 and 2016 studies. However, offline issues had a high correlation with false positive quarantining and are likely to have caused significant delays during offline periods. Finally, the improvements in this study demonstrate that decommissioning at the checking stage can work and in turn provide key information to professional staff at a suitable time. Systems and change management strategies which have been proven to be successful in similar contexts could be implemented to ensure that HIT's are rolled-out effectively to facilitate staff adherence, adoption and engagement. Chapter six conducts qualitative interviews to learn more about key issues raised during this and previous chapters. The aim of chapter six will be to gain qualitative data to learn more about health information alerts and to support the quantitative results seen in chapters three and five.

6.0: The Effectiveness of Health Information Technology Alerts in the Digital Medicines Screening Technology Context: A Qualitative Study

6.1: Introduction

The effectiveness of digital alerts in healthcare information technology (HIT) systems are poorly evidenced in the literature. Shojania et al. (118) explain in a systematic review that "home-grown" and "active" alerts demonstrate some marginal evidence of improved effectiveness compared to other point of care reminders but there is a lack of studies which investigated the effectiveness of HIT alerts.

Chapter five involved the implementation of a home-grown audio alert at the point of medicine verification and suggested reasons for an improvement in detection and authentication rates when compared to the same technology in chapter three. This study aims to use qualitative methods to explore the findings of chapter three and five further and to compare the quantitative results in chapter five to the qualitative results obtained during participant interviewing in this chapter. This chapter identifies the key themes that emerged throughout qualitative interviews and understands staff perspectives on the technological change as well as other system or behavioural changes that occurred.

Qualitative interviews were conducted with participants who had been part of three studies. 1. Using a medicines authentication technology (MAT) without an audio alert (Chapter three). 2 a Delphi method study which involved suggestions for improving the technology (Chapter four) and 3. Using a MAT with a user instigated audio alert (Chapter five). This

chapter is based on the pharmacy context but is expected to represent how healthcare staff interact with audio alerts in the wider healthcare environment. The outcomes of this chapter may also be relevant to other industries where digital information alerts are used.

6.2: Methods

Qualitative interviews were conducted three days after the completion of the chapter five study. Conducting interviews shortly after the final study ensured that the thoughts and opinions of the staff were current. Ten staff members were interviewed individually over three days. The interviews were held in the same room under the same conditions, using an interview guide (**Appendix 6.0**). Eight of the participants had been involved in all previous studies (Chapter three, four and five), and two of the participants had experience using the technology with the audio feature only (Chapter five). Question one to six, and question 22 form the interview guide were demographic or closed questions and were not included in the thematic analysis but instead displayed as a frequency in **Table 6.0**. Interviews were recorded using a hand-held voice recording device, transcribed into a word document and entered into the Nvivo system for thematic analysis. Manuscripts were anonymised by coder A (BN) by removing any reference to participant, brand or company names. Coder A then read each manuscript, recorded a list of themes and coded for those themes using the Nvivo software package. These themes were shared with coder B (LR) who carried out a further coding process, altering themes and subthemes throughout. Both coder A and B discussed the themes and subthemes and agreed on those described in **Table 6.1**.

Coder A then re-coded the manuscripts in light of the agreed themes and subthemes. Interrater reliability was conducted with Kappa statistics (**Table 6.2**) using Nvivo software, with calculations based on the frequency of characters. Participant names, product brand names and company names were removed from all quotes. Product names were replaced with generic names. E.g. Nexium® would have been replaced with esomeprazole.

6.3: Ethical Approvals

This study was classified as research according to NIHR guideline's and as such required ethical approvals which can be found in Appendix 4.0. (p 290.) HRA approval and Trust R&D approvals were also required which can also be found in Appendix 4.0. (p293 and p294).

6.4:Results

Table 6.0: Staff group demographics gathered from questions one to six.

No	Age	Sex	Healthcare Experience (Years)	Current Role	Experience using technology before audio adjustment	Experience using the technology with audio alert
1	Anon.	F	Anon.	ACT	Yes	Yes
2	Anon.	F	Anon.	ACT	Yes	Yes
3	Anon.	F	Anon.	ACT	Yes	Yes
4	Anon.	F	Anon.	Pharm.	No	Yes
5	Anon.	F	Anon.	ACT	Yes	Yes
6	Anon.	F	Anon.	ACT	Yes	Yes
7	Anon.	F	Anon.	Pharm.	No	Yes
8	Anon.	F	Anon.	ACT	Yes	Yes
9	Anon.	F	Anon.	ACT	Yes	Yes
10	Anon.	F	Anon.	ACT	Yes	Yes
	41.6 (Mean)	F (Mode)	16.9 (Mean)	ACT (Mode)	Yes (Mode)	Yes (Mode)

Further to Table 6.0 as a response to question 22, all participants explained that the introduction of the audio alert had a positive impact on the detection of poor quality medicines. When participants were asked who initiated the idea or suggested altering the technology, participants involved in chapter three, four and five studies successfully identified themselves as the group that suggested the implemented audio alert, i.e. not an external manager or the researcher.

Table 6.1: Themes and subthemes identified during thematic analysis.

	Themes in bold and subthemes in italics
A	**The effect of an audio alert on behaviour** *1 The characteristics of the audio alert* *2 The effect of the audio alert on adherence to policy* *3 Auto piloting; positive and negative*
B	**Point of care alert appearance and characteristics** 1 *Coloured pop-ups* *2 Point of care alert characteristics*
C	**Learning and peer influence** *1 Protocols* *2 Errors* *3 Peer influence*
D	**Impact of the technology** *1 On the individual* *2 On the workforce* *3 On the workplace processes, e.g. controlled drug supply*
E	**Technology performance issues**

Table 6.2: The main themes and subthemes with corresponding kappa statistic and percentage levels of agreement or disagreement.

Key Themes / Sub-themes	Kappa Statistic (characters)	Agreement (%)	Disagreement (%)
The effect of an audio alert on behaviour	0.77	95.77	4.23
Auto-piloting	0.72	95.33	4.68
Point of care alert characteristics	0.78	98.47	1.53
Coloured pop-ups	0.94	99.78	0.22
Learning and peer influence	0.74	95.18	4.82
Impact of the technology	0.80	95.39	4.61
Technology performance issues	0.73	99.17	0.83

6.4.1: The Effect of an Audio Alert on Behaviour (A)

The Characteristics of the Audio Alert (A1)

The consensus regarding the effectiveness of the sound used for this study was positive and was captured by the following quotes (A1,1-3).

1. *"It's not annoying, it's not too piercing or anything like that, and it does encourage you to take action" [P1]*
2. *"Well, no. It's effective. The only thing it really sounds like is the call button in the nurses' station [oh, okay], so that was a little bit confusing, to begin with. But it's a distinctive sound, and it's a sound that now, to me, you just associate it with that [okay]. So, that's quite helpful. It's not a sound I'd mix up with any other audio alerts for anything else."[P5]*
3. *You associate that sound with something that you need to look at [P1]*
4. *"It's just an extra – it's a buffer; it's a safety net. It's another clue that there's something to look out for' [P5].*

A1,1-4 are representative of the cohort where 10 out of 10 participants described the audio alert generally as having a positive impact on the technology. The unique nature of the technical sound appeared to be beneficial within the hospital context and was described as *"different ....to anything else"*. Furthermore, it was clear from some of the comments that

prioritisation was key in relation to alerts. If one task was deemed more important than another then that took preference (A1,5-6).

5. *"there are times when it is busy and you just have to do what you can for the patients, and other things take a bit of a back seat if you don't perceive them to be as important as the patient" [P5]*
6. *"And on the urgency of what you're doing. It was perhaps also because it's … it's not as important as getting the drug at that time to the patient. I'm not saying it's not important, but it's—" [P5]*

The Effect of the Alert on Adherence to Policy (A2)

Throughout the interviews, the frequency of the sound was explained to play a part in how staff members responded to alerts (A2,7). Furthermore, it was explained by all participants that this was not a sound which the staff ignored or imagined could be ignored (A2,8). The cohort implied that perceived sophistication of the alert system affected user compliance (A2,9).

7. "*Very infrequent. But then I hadn't used the system very many times. I think it was the fact that when you did get an alert, it meant something" [P6]*
8. *"No, I don't think I've ever ignored it" [P7]*
9. *"The first time I used it, it didn't feel so sophisticated. It seems strange that an audio alert, can make a system more sophisticated, but that's what I thought" [P6]*

One participant explains that humans are becoming more attached to their smartphones and cannot stop themselves from checking their smartphone when it sends an audio alert (A2, 10). This participant eludes to the fact that this behaviour may be affecting the behaviour associated with how we respond to other audio alerts and that maybe one's response to audio alerts is now different to before. The policy in this study was to quarantine a product when an alert sounded. If the staff were more

sensitive to audio alerts, this may have facilitated an improved adherence to policy.

> *10. "…..if your phone buzzes, oh what's that, what's going on, what's happening? And so, your natural instinct is to find out what that noise is, so I think having a noise certainly improves the amount of people that are going to be looking at it so your results are going to be better" [P3]*

Staff members that worked across different sites explained that an audio alert may not always be effective at helping staff adhere to work policy, especially in a working environment which is noisy or already has multiple sound alerts. During the interviews, two separate staff, both of whom who worked across different sites suggested a vibrating hand-held scanner or keyboard could be useful for larger sites with higher noise levels or competing for audio alerts (A2, 11).

> *11. "But the keyboard could vibrate, or the scanner could vibrate when you scan something that's a product that shouldn't…. A bit like when you're using a game console you get a rumble on your controller" [P6]*

<u>Auto-Piloting (A3)</u>

A theme which arose throughout the interviews was the concept of auto-piloting in the workplace. The repetitive nature of scanning drugs itself was perceived as likely to cause staff to "zone out" or "switch into auto-pilot", a process which the participants explained was often broken by the active audio alert (A3, 12 -14).

> *12. "I think so. When you're doing a job that's repetitive, you do tend to switch off and— It's like driving a car, isn't it? After a period of time, you just get used to things, and you don't think about them. Then you have to tune back in, in certain circumstances. The audio makes you (tune) back in, I think" [P5]*

13. *“Yeah, it stopped you doing so much on automatic pilot, I think” [P5]*
14. *“…….When you’re undertaking a process, it can become quite easy to just do that process and not think through the reason for that process taking place. It becomes like an auto-pilot and you’re just going through the motions. Whereas if you go through the motion and get an audio alert, it makes you think that you need to act.” [P6]*

Furthermore, it appears that the sound reduces the risk of auto-piloting by adding priority to the pop-up alert and reducing the risk of alert fatigue A3,15-18.

15. *"Some things just flash up on your screen like pop-ups and things on computers, and you're just instantly closing them aren't you because you don't see that they're of any importance but as soon as a noise is generated somehow change the dimension of what that message is" [P3]*
16. *"I've had pop-ups with noises, and I've gone, oh, what's that? And I've looked, and it's drawn me in a little bit more than just closing down a window as it flashes and gets in my way." [P3]*
17. *"I think the sound is good at notifying you to look at the pop-up, I think that's if you didn't have the sound you perhaps wouldn't pay as much attention to it but because it's got the sound you think oh, I need to look at that" [P1]*
18. *“Fact I heard a noise that made me look at what happened, what that noise was all about made me then see the pop-up and what had all gone on and so yeah, I think it's positive" [P3]*

Auto piloting was observed in two distinct categories, individual auto piloting and team auto piloting. Individual auto piloting had either a positive or a negative outcome and team auto-piloting was observed as being positive.

Positive individual autopilot

One of the users made an argument that the dispensing process needs to be quick and authenticating medicines should not be a time-consuming task. The participants explained that an audio alert allowed them to scan medicines on auto-pilot and use the active audio alert as a

trigger to act, therefore streamlining the process (A3,19) and removing the time pressure of checking the on-screen alert (A3,20-24). There was a consensus amongst the group that auto-piloting streamlined the process and improved efficiency in the presence of an audio alert.

19. *".... it was quite easy just to go scan, scan, scan, scan and just go through the whole lot" [P5]*
20. *"I felt reassured that there was a sound, which took some of the pressure off me having to make sure I'd checked any pop-ups that would have come up on the screen" [P6]*
21. *"It felt easier to be given an audio alert rather than having to read something off a screen" [P6]*
22. *"When you've got a whole tray of stuff, and you've got several things in there that need to be scanned, you can just zap it without having to check the screen every time. You're not constantly having to look up at the screen, you just hear the alert and know that…. It's like scanning it through in the supermarket" [P8]*
23. *"When you've got a busy screen; you're looking at your prescription, you're looking at the product, you've got a screen, so three different places, and then you look at another screen to track out the prescription. There are a lot of things to remember and having that prompt – because it's a noise – takes away some of the pressure of having to read off a screen." [P6]*
24. *"It's doing the hard work for you, isn't it? It's alerting you to the fact that there's something wrong, whereas otherwise, you've got to rely on you actually seeing it on the screen. So, if it's making a noise, there's a problem with it, whereas before it would just pop up and if you weren't 100% on it, that's nearly missed." [P2]*

Negative Individual Auto-piloting

Participants explained that in a busy environment it was easy to scan medicines on autopilot and forget to look at the screen (A2, 25). This may have been aggravated by the use of a hand-held scanning device with a large cord which facilitates the scanning of a product at a distance from the screen during the medicine checking process in the dispensary.

25. *"...if you had a pop up before you might be so busy that you just look at it and think oh yeah, there's a pop-up, whereas a*

noise will definitely alert you that you need to do something…" [P1]

It was explained by one participant that the audio alert broke the operator out of the 'auto-piloting' mode associated with the systematic scanning of medicines. However, the opposite of this scenario could be that over-reliance on a sound alert may also encourage staff to pay less attention to on-scree computer alerts (A2,26).

26. "I'm worried that I missed something because I wasn't looking at the screen. [P9]

Team Auto-piloting

Another concept appeared which related to professional obligation and how the noise not only reduced auto-piloting by the individual but also by an observer or a staff member in the vicinity who may not have been in direct sight of the operator or scanning terminal (A2, 27).

27. "I think it was positive although I don't think I ever scanned one that came up with an alert saying this is falsified but I heard someone else's and that made me look up and think, what was that? So, I noticed when there was a falsified one?" [P4]

Regarding auto-piloting, it reduced the likelihood of the user and the team missing the alert. It was clear from the interviews that having a sound alert encouraged better teamwork. It drew attention to the staff of all experience levels who may have required help (A2, 28).

28. "I think it encouraged us to do it and I think the fact that the first time I think for most people they got that, oh it's made a noise what do I do, once you've done that you knew because everybody realised that, I think most people's attention was probably drawn to it by people going, oh it's made a noise rather than the noise itself so then somebody could sort of help you to show you what to do" [10]

6.4.2: Point of Care Alert Appearance and Characteristics (B)

Coloured Pop-Ups (B1)

Throughout the interviews, participants explained that there was confusion between the two amber pop-ups that could occur. Although they contained different written information requiring two different actions (Quarantine and dispensing) the staff identified that they would often look at the amber response and dispense without reading the text on the alert (B1,1).

1. *"Yeah [yeah]. You know when the things pop up, and it says, 'authenticated here,' [yeah] and 'authenticated elsewhere?' [Yeah.] My recollection is that they're the same colour [that's correct] and I think I've probably missed because I've just looked 'read – authenticated,' and assumed it would be 'authenticated here,' so just dismissed it [okay]. So, I think they should be different colours…" [P2]*

For any pop-ups that were amber irrespective of the product requiring quarantine or not the amber pop-ups were largely closed and ignored. There was confusion between the two amber alerts because the operators looked at the pop-up colour and not the text information within the alerts. This resulted in medicines requiring quarantine being mistaken for those already dispensed on-site (B1, 2). One of the participants went on to say explicitly that the alert associated with medicines "Already authenticated here" should be a different colour to those authenticated elsewhere (falsified) (B1,1) (B1,3).

2. *"No I didn't find it confusing, I just always had to take a, like when it came up in red you knew straight away that you needed to do something whereas if it was an orange alert you did a bit more of a double take to see what it was coming up on the screen whereas*

if it was red you knew automatically what you needed to do with that" [P1]

3. *"Because when it makes a noise you look at it, and it says authenticated, but it's orange. So, if it said authenticated and it was orange, then it's an authenticated here. If it said authenticated and it was green, 'Oh, that's elsewhere.' Do you know what I mean? [Yeah.] So, I don't think you would mistake them so much." [P2]*

Point of Care Alert Characteristics (B2)

When participants asked to compare the audio and visual alerts in this technology, i.e. coloured pop-up alerts and an audio alert with other alerts they are exposed to in their working environment the staff referred to a number of technologies present in their workplace. The comparable alert technologies included the patient medication record (PMR) system, the electronic prescribing record system (EPR), a medicine fridge alert system which monitors temperature (FAS), and desktop computer calendar alerts (CA). The perceived effectiveness of an alert within these technologies was affected by a number of factors. These factors included the amount of information contained within the alert, and the faith the staff members had in the alert, i.e. Staff in this study explained that an alert which is known often to be inaccurate or out of date is often ignored (B2, 4-7).

4. *"Also, you know that the information is up to date and current whereas we can get error messages on PMR or information that pops up on the PMR and you know that half the time it's out of date information, so you don't always pay attention to things like that." [P1]*
5. *"Yeah, we've had a couple of checking errors made where somebody has ignored the pop-up." [P10] (Referring to the PMR system)*
6. *"There are too many, and they get ignored, I think, particularly with PMR. It's because they're not managed properly; they should*

be— You get used to things being out of date and not needing to pay attention, so you stop paying attention completely." [P5]

7. *"I think this is better because you get that noise, I think perhaps if you had a noise with PMR it might be a slightly more yeah, but I think some of those pop-ups on PMR are so old that's why people ignore them, they don't get taken off when it's not apparent anymore, or it's not applicable do they." [P10]*

The audio alert and colour coded alert combination seen in the MAT facilitated staff to react appropriately to alerts (B2, 8-9).

8. *"I think these are better because the pop-ups are colour coded as well so you know that you need to pay attention to especially the expired and things like that, you know that you need to pay attention" [P1]*
9. *"Because it alerts you to the screen, I think the last one just flashed up didn't it and I think some things just flash up on your screen like pop-ups and things on computers and you're just instantly closing them aren't you because you don't see that they're of any importance but as soon as a noise is generated somehow change the dimension of what that message is, I've had pop-ups with noises, and I've gone, oh, what's that? And I've looked, and it's drawn me in a little bit more than just closing down a window as it flashes and gets in my way, closes it off, needs to move on." [P3]*

Existing alerts within the workplace may have an impact on how effective new alert technologies such as MAT's are, alerts such as a fridge temperature monitor alarms, doorbell's or alerting robotics may affect the usefulness of new audio alerts, however in this study the MAT alert was effective due to the lack of other major audio alerts in the study setting (B2, 10).

10. *"No, I don't think so. It's nothing like we've got in there at the moment. There's no noise that makes something like that, that bleeps or anything. It's not like working with a robot, where it makes different noises. It might be a different kettle of fish then. But in ours, it's quite quiet, isn't it? So, yeah." [P2]*

Some working environments contain many alert technologies. In these circumstances the staff have suggested useful differentials to fight "alert

fatigue". These suggestions included a vibrating hand-held scanner or keyboard (B2,11) as mentioned previously.

11. *"But the keyboard could vibrate or the scanner could vibrate when you scan something that's a product that shouldn't…. A bit like when you're using a play station, you get a rumble on your controller" [P6]*

When comparing pop-ups alone with pop-ups with audio alerts, it became apparent that the operator prefers the audio prompt within this working environment (B2, 12).

12. *"I think with screen alerts you can just very easily get rid of them and you just kind of bypass them whereas with a noise that makes you stop for a moment I think so I think that's a bit more useful." [P4]*

The message contained within a pop up also appears to be important (B2, 13-14), the volume of data and how often the same message is repeated (B2, 15) also has an impact on how likely one is to act on that alert.

13. *"I think this one was better because there were less words to it, it was a lot more of a sharper statement so you could quickly just glance at it and know what it said rather than on EPR you have to read a massive paragraph." [P4]*
14. *"I use EPR, and we get pop-ups on EPR. I find them quite frustrating because there's always a lot of information in the pop-up…..often it's the same message time and time again…..you read it the first time and then close it down. The next time there's a pop-up you think you've seen that one before, so you just close it down rather than automatically reading it through from beginning to end because something may have changed." [P6]*
15. *"With this, it only comes up when you need to make an action, so it's not irritating, whereas the ones on EPR tend to come up constantly and so you're more likely to click through them. With this one, you know you need to action something." [P7]*

When asked how the pop-ups with or without audio compared to other alert tools within the department the staff explained that a pop-up calendar reminder with an audio alert is very effective, but without an audio alert

this reminder is less effective (B2, 16). Audio alerts have been explained to be more effective when they are not constantly alarming and that constant alarming leads to the alert being ignored (B2,17-20).

16. *"In terms of other pop-ups, I see, I guess the calendar alert pop-up and a bell that chimes in the background is the one that I see most often. It's reminding me that in 15 minutes I've got an appointment or a meeting. I always respond to that because it's a noise. But if I've got my sound turned off on my PC, if it pops up I wouldn't automatically look at it because I have so many things popping up on my computer all the time. Pop-ups happen on your PC a lot of the time for different things and because you use the internet a lot outside of work, if you have pop-ups then often it's an advertisement that you automatically want to close down. Having a noise with it is a different kind of stimulus for reacting to it." [P6]*
17. *"I don't think PMR makes a noise does it, so it just flashes up as it were but I think a lot of people do ignore that, we try and discourage people from ignoring it. And the only other noise I can think of is that everybody ignores "Fridge Alert System (FAS) don't they, FAS can go on for quite a while without anyone actually going, what's that noise. You don't seem to notice it straight away do you whereas you do notice" [P10]*
18. "*I think this is louder isn't, it but it's not too loud for anybody else if you know what I mean, trying to think now I just know that I never notice FAS until it's been going for some time*." [P10]

6.4.3: Learning and Peer Influence (C)

Protocols (C1)

There were examples where staff explained that they learned and adapted to new technology in different ways. Some explained that they learned as they went along, some felt that repetition was the best way to learn, and although the majority of participants seemed dis-incentivised by protocols. The concept that protocols are ignored or undervalued is echoed throughout many of the interviews (C1,1-3).

1. *"I didn't feel like I needed to continue to refer to the protocol I think once I read it and carried out the process a few times it wasn't something that I felt I needed to refer back to." [P1]*
2. *"I think yeah, who likes reading protocols, SOPs but they're one of those things that has to be done, and I don't know, you could have perhaps had a log for people to sign after they've read the protocol or did you do that, I can't remember if you did that?" [P3]*
3. *"I think protocols are quite difficult to read on their own so I think you kind of need to read it alongside while you're doing things so you understand why the protocol is there so I can understand that when it's quiet you don't have the work to generate a problem to investigate so then you think ah, this is what we need to do and then you can read from the first protocol, so I do understand that." [P4]*

Despite the general consensus that protocols are not positively accepted there was a small proportion of staff that were quite happy to conform to the employer's protocol requirements (C1, 4-5).

4. *"No, I think you should still read the protocol when you're busy because even if you're busy, you should be doing what the protocol is saying so I think you should be doing that anyway" [P4]*
5. *"I would probably agree that you don't have time to read the protocol when it's busy. But I would also say that if you've signed up for the study, then you should have read it prior to it being busy or you're doing your checking slot." [P7]*

In relation to the concept of learning through repetition, it was clear that at least a subsection of participants placed priority on repetition as the most effective way to learn how to use a new technology (C1, 6 and 8). Others were referred to as being "on the job learners" (C1, 7).

6. "By repeating it. Repetition" [P2]
7. *"Yeah. It's a funny thing, isn't it? A lot of those are on-the-job learners [right]. So, you're learning about something, and you do it, but to read through something without applying it at the time doesn't stick, does it" [P5]*
8. *"I'd say the best way with this kind of thing is to read it, do it, and read it again [okay], once you know what the job is." [P5]*

Time to reflect upon the technology was described as being more useful than the time physically using the technology. Quotes (C1,9-10) echo the

reflective thought process of a typical pharmacist or accuracy checking technician.

9. *"I think reflecting probably made me think I remembered this from last time" [P6]*

10. *"Usually in terms of the technical medicine checking process, technical checkers are allowed the freedom to learn a new way of operating as opposed to being prescribed the best process by a senior."*

There was a perception that training in the second study was different or improved, despite it being identical to the first stage. (C1,11-13).

11. *"I think the difference was the training was slightly more robust in the second study, in terms of the information we were provided with." [P6]*
12. *"I think the information provided the second time around had more pictures on. I don't know if it did or whether I'm making that up, but that's what I seem to remember." [P6]*
13. *"You went through a more thorough training thing this time." [P5]*

It was also clear that being involved in changing the approach of the study may have encouraged better co-operation and buy-in (C1, 14-5).

14. *"I think the second time around people were more aware that the study was happening and that they needed to participate in it. I know that they knew they needed to participate in the first study, but people took more responsibility the second time than they did the first time." [P6]*

15. *"I suppose if you've suggested something you think it's going to work and, yeah, you're probably more likely to make it work, aren't you [laughs]. I don't know. But also, if you think it's going to work, it probably will [okay]. If you ask the people who were doing the job, they tend to be the people with, I would say, the better ideas, because they're doing it day in, day out." [P5]*

At the end of the eight-week study in chapter 5, all of the participants could explain that the inclusion of a sound was their idea.

Errors (C2)

The participants explained that errors, if they occurred, were not intentional. Although this is an expected result to such a question, they did admit to some errors in scanning (C2, 16-19).

16. *"I don't think there was an occasion where I knew it needed to be scanned and didn't scan it intentionally because it was busy or anything like that, I know that there was a situation where after I'd checked and handed something out I realise that I should have yeah but unintentionally but not intentionally."*
17. *"I know the reason why I didn't end up scanning that is because I was rushing when I was checking it because it was an outpatient had been waiting so long, so it's just the situation in dispensary and don't know, could take more time over my checking but then I'm also conscious that the patients have been waiting longer than the turnaround time so…" [P1]*
18. *"I think I very nearly didn't scan something and then realised that it had to be." [P4]*
19. *"I think I didn't realise they needed to be scanned, but then for some reason I suddenly thought, oh wait, that might be one that needed to be scanned and it was so then I scanned it…" [P4]*

When using the MAT, the staff developed a workaround. When a medicine with a 2D data matrix was scanned, the 2D barcode was crossed through with a pen. Placing a cross through the 2D barcode rendered the matrix un-readable (C2, 20). Often workarounds are necessary and inventive. However, it remains to be seen whether this workaround will be useful or not during full FMD rollout.

20. *"I think since then dispensary is putting a cross through that sticker so it's already been scanned out at the OUH so when it's first authenticated at the system the checker should put a cross through so then if you're re-using the part pack you know it's already gone through the system." [P3]*

Peer Influence (C3)

The audio alert was not ignored intentionally, and actually, the audio alert had a positive impact on the team (C3, 21). When the alert sounded, which was only 4% of study cases not only did it draw the attention of the operator but it also raised the attention of the sounding workers which facilitated co-operation.

21. *"Never ignored as far as I'm aware [really] because it was a case of, 'Oh, what have you got?' [Yeah.] And that was not only the person checking, that was anybody around it. It was a bit of a, 'Oooh, what have you got then?' So, a bit of a competition to see who got the best thing [right]. Does that make sense?" [P2]*

The following quote (C3, 22) is in relation to authenticating medicines (C3, 22).

22. *"It was a bit of a competition to see who got the best thing." [P2]*

In response to the question, how did it feel when you were someone who was on the outside? So, you hadn't scanned it, but you had heard the following comments were made. It was clear that peer influence was positive from a learning perspective (C3, 23-26).

23. *"…when the audio went off, people's ears pricked up and they came over and looked at the screen. Whether that was because they felt my experience was lesser than theirs and they wanted to make sure that I was dealing with it correctly…. Which I suspected they were. I found it quite reassuring that I'd got support if I needed support." [P6]*
24. *"I think it's positive. It made me think that everybody is now thinking that this is important, some action needs to be taken, and we're all responsible." [P6]*
25. *"If anyone else was using it and it made a noise and they looked at it a bit blankly I think people would sort of help other people too, oh you've just got to do that, you've just got to write down what it says or whatever." [P10]*
26. *"Yeah, I suppose it also would alert, if somebody else was checking alongside you and they chose to ignore the noise you would hear the noise and say to them that noise is there for a reason, you've got to do something about it wouldn't you. So actually, if it was an*

accredited checking process you would know that that person whether they'd done that or not wouldn't you if you were the person doing their exam at the end because that's what we do we would watch somebody checking something so you would be alerted as well wouldn't you." [P10]

6.4.4: Impact of the Technology (D)

On the Individual (D1)

This technology had an impact on the individual and the team or the work environment processes. It was observed that the authentication process became part of the individual's routine and didn't appear to be a cumbersome or onerous task. The quarantine process was also not considered as being cumbersome due to the low volume of alerts. Furthermore, following completion of the study participants expressed a wish to continue with the MAT and new alert. They expressed the opinion that authentication became habitual and they missed the process as part of their working day (D1, 1-4).

1. *"No. Just was better, seemed to flow, soon got into it. You know, a couple of days in, you were sort of, like, just looking for it really. Now it's stopped, you're looking to see, 'Oh, this did have a label on it, and it hasn't [laughs].' So, yes." [P2]*
2. *"No because if you're actively doing something, and if this is part of the process that needs to be drawn in then it's going to become part of your practice, I mean the fact is that if it alerts and it's expired, or it's not authentic then it just goes into a bin, and it's someone else's job to deal with that rather than so yeah." [P3]*
3. *"Yeah because you want to know whether this one is the dodgy one or not don't you [okay] and then it's not too much trouble is it because if you do get one that flags up as being unauthenticated like I said your just putting it into a box and it's dealt with by someone else, so it's not hindering you any further in terms of you then have to go and do this process and that process." [P3]*
4. *"I wanted to know what it was, so why did it buzz, what was that and then it told me it was already dispensed at the OUH and I went okay, so that's what it was, fine, don't need to do anything else, case closed." [P3]*

The MAT was perceived to be a positive aid to the individual during their working day. Despite the MAT system being described by one individual as being initially 'overwhelming' (D1, 5).

5. *"I think within the first eight weeks, I felt a little bit overwhelmed by the steps I needed to do to check the product. I felt pressure on checking the product and knowing I'd still got to put it through the system, to make sure that there weren't any alerts that came up on that. The second time around, I felt more aware that there are products elsewhere in the department, other than just in the dispensary as well, that would have stickers on. Like in the CD room, where you might have to bring something out of the CD room and into the dispensary and scan it through the MAT system there." [P6]*

The time of day may a risk to verification compliance. When there is a pressure to complete dispensary work for the day, and workload is high. Working is likely to be rushed which may affect compliance, especially for part time staff that will be less exposed to the technology and how to react to alert which are likely to be infrequent (D1, 7).

6. (Part-time onsite staff member) "I don't know whether that's because of the way my checking slots fell. Quite often my checking slots would be I'd go in at the end of the day to help support finishing off work. When you're put in a system where it's the end of the day, and the work has got to be clear, you don't have time to reflect; you just do it. If I'd had a more structured checking slot, I think I would have come up with that solution (The best way to scan medicines) sooner because it was part of my process and my checking slot. I would have felt less pressure to come up with a solution, whereas at the end of the day you just feel pressured to support getting work through." [P6]

Effect of the technology on the individuals checking process was mixed. Feeding once again into the theme of learning, one participant explained that reflecting on their work processes was useful (D1, 7). Some staff explained that there was a limited effect and as discussed previously, the authentication process became habitual with some experiencing

trouble re-adjusting. Participants explained that this had a positive impact on their checking process when compared to the technology without the sound as it took away some pressure to stay tuned into the on-screen alert (D1, 8-10).

7. *"I think reflecting probably made me think I remembered this from last time. It didn't necessarily feel that streamlined in terms of how I work. When I do a piece of work, I like to work through a process and know I've done that process correctly. I find it very chaotic if I don't have that structure. I guess I wanted to introduce that structure myself so that there was a process I could follow and get rid of the risk of interjection of errors or chaos." [P6]*
8. *"It takes the responsibility away from you having to make the decision to stand and read it or go and check this when I know I've got the rest of the checking bench……?" [P6]*
9. *"Having the prompt took away the fact that you didn't need to read a lengthy procedure or protocol." [P6]*
10. *"It helped. I think if it wasn't there I would have scanned the items out and then may have just put them through without noticing a visual pop-up because it's on a different computer system than what I'm scanning out on and checking on."*

<u>On the Workforce (D2)</u>

There was a perception by the workforce as a group that this HIT impacted them as a group. When using the technology one staff member documented that they often forgot to scan the controlled drugs. This comment was fed back to staff during the qualitative interviews. In relation to the workforce dispensing Controlled Drugs (CD's), they explained that CD's located in the separate CD room were missed due to the distant between the MAT terminal and the CD room (D2, 11-14).

11. *"Yeah, I think I agree with that but not necessarily because of the extra checks but because there isn't a scanner in the CD room, I think probably CD were missed because when you're checking the CDs you have then got to take them out of the CD room to scan them, and if you were checking the CDs on the checking bench then I think you'd remember but because it's disrupting your normal process for checking I think probably I think there were more that were missed." [P1]*

12. *"When it goes live properly, you'll probably need an extra scanning thing in the CD room to make that easier [okay, yeah] because you've also, physically, got to travel a bit of a distance from the CD room and so on." [P5]*
13. *"I had to, I went back into a few bags afterwards, I don't know if that was because I was going into another area away from the check-in, but there was sometimes when I almost missed like the [7:58 – inaudible] was it on codeine as well?" [P9]*
14. *"Yeah that was me because you are going in there, you are checking the CD register, you're checking for the working copy, and then you come back out and put it in the bag, and you forget yeah I did really find it difficult with CD's." [P9]*

On the Work Processes (D3)

As explained previously the staff became 'habitual' scanners and even after the study was complete they explained that they were looking for products to scan (D3, 15).

15. *No, I think we just got into a habitual scanning didn't we really." [P10]*

The operators felt that there would be little interruption in their workflow and that scanning would eventually become part of the process; with some taking longer to adopt than others (D3, 16-19).

16. *"During the first study my process was to check as normal but put the ones that I needed to scan to one side and scan them at the end whereas this time I decided to do it differently and scan each item as I went along so if I found that it needed scanning I would do it at that point instead of putting them all to one side. I think before I felt like it was disrupting my process to scan during my checking, but this time I think perhaps because I've been checking longer I felt more comfortable to do that, so I don't think it…" [P1]*
17. *"I think the first time I decided that scanning during my checking would disrupt my checking so I decided to put them to one side and scan at the end, so it didn't disrupt, but this time I don't know, maybe I felt more comfortable with the process but then I decided that actually, it wasn't really that disrupting, I just made sure that I was checking next to the scanner on some occasions you might be a bit further down the bench and have people putting stuff in front of you so." [P1]*
18. *"The second time around, I don't necessarily think it did have an impact on workflow because it just became part of the checking process. The first time around, because I didn't have a process, it*

felt like it was a big ask as part of the work that you were doing already" [P6]

19. *"I don't think it's not necessarily something that we can't do it because I think it's just a case that we would all have to review our process and think which way round was the best place to have the scan so is it best to do it at the end or as you're actually just checking." [P9]*

6.4.5: Technology Performance Issues (E)

There was a noticeable issue with offline errors observed in the chapter five study. An offline error refers to an occasion when a medicine is scanned, and the scan fails to be verified against the NMVS database due to a drop in database internet connection. The organisation monitoring and maintaining the database were aware of this issue. When frequent offline issues were identified to the organisation overseeing the NMVS database, they were already aware of the issue as it was affecting their European clients. During chapter three and five studies, staff volunteered feedback and this feedback was put to the staff during these interviews. The following comment was made by one staff member '*The most annoying thing is the offline error when you have to keep scanning*' The following responses were volunteered by the participants and were representative of the group (E, 1-7).

1. *"That is annoying" [P9]*
2. *"Yeah, I did, and there were a couple of occasions when I'd have to scan something a few times before I'd finally get it to go through which was a bit annoying." [P1]*
3. *"I didn't, no I've heard people talk about that." [P3]*
4. *"Well, it was annoying, but it's technology, and you have glitches, yeah." [P5]*
5. *"It was that common for a short period of time, [okay] and then it was resolved and it was fine."*
6. *"That was really annoying. But then sometimes when you scanned it again you'd still get the error, but if you scanned it again, it would be fine. But I suppose if it's offline it comes back online*

again. That was a very irritating noise that certainly drew your attention to the fact something wasn't right." [P8]

7. *"We only had a couple of instances where it went off, and then there was, in the beginning, it went off but it wasn't an actual, I don't know was there a hiccup at the start I can't remember?" [P9]*

Table 6.3: Summary of considerations for the research, design and implementation of MAT's and HIT alerts more generally, categorised by theme.

Summary of Chapter Six Findings
1 The characteristics of an audio alert
The technical parameters of an audio alert should be user-friendly
Compliance with the alert will be affected by how staff prioritise the alert within their unique context
2 The effect of an audio alert on adherence to policy
The frequency of the audio alert may affect whether or not the alert is ignored
The perceived level of sophistication may affect alert adherence
Those that use smartphones may to be more curious about audio alerts than those that do not
New alerts may be influenced by other sounds in the environment
Vibrating hardware could prove useful in a noisy or multi-alert working environment
3 Auto piloting; Positive and negative
An audio alert adds priority to an information pop-up and reduces an individual user 'Auto piloting'
An audio alert helps to reduce alert fatigue
An audio alert brings the incident to the attention of a supervisor or colleague which facilitates user learning and support while reducing the risk of the alert being ignored
Point of care alert appearance and characteristics
1 ***Coloured pop-ups***
Colours presented should be distinctive to prevent confusion
When colours and text are presented the text is often ignored, and actions are based on pop-up colour. Therefore, a written message alone shouldn't be relied upon.
2 Point of care alert characteristics

Compliance is increased when pop-ups are perceived to be up to date, and the user has faith in the information provided
A pop-up alert is most effective if combined with a suitable audio alert
Existing audio alerts within the environment are likely to influence the success of a new audio alert
Frequent repetition of alerts may encourage the user to ignore all such alerts
The desktop calendar alert is a good example of a well adhered to audio and pop-up alert
Learning and peer influence
1 Protocols
Repetition and time to reflect on the new process encourages learning in relation to new technologies
Protocols alone are not adequate learning tools
2 Errors
Users do not knowingly or intentionally make errors
Placing priority on one task above another leads to errors in low priority tasks
Workarounds are likely to occur in a new system or technology; these can be inventive and useful in some circumstances
3 Peer Influence
An audio alert puts pressure on the user to act upon the alert
An audio alert encourages surrounding staff to help the user with the process, providing help and guidance
Impact of the technology
1 On the individual
Although initially overwhelming medicine authentication becomes 'Habitual scanning" within eight weeks
Part-time staff working irregular hours may result in poor compliance with low-frequency HIT alerts
2 On the workforce
A technology for authentication medicines needs to be located within all dispensing rooms to perform a final checking process, i.e. controlled drug room

Technology performance issues
Offline errors at a frequency of 4.67% caused notable disruption to workflow

The themes discussed throughout these interviews have highlighted a number of research, implementation, and design considerations for MAT and HIT alerts and are summarised in **Table 6.3**.

6.5: Discussion

6.5.1: The Effect of an Audio Alert on Behaviour (A)

The Characteristics of the Audio Alert (A1)

The technical sound deployed in this study was a sine waveform, with a frequency of 530 hertz and sound length of 1 second, with the volume being between 90 and 98 decibels. This sound was well accepted by the staff and described as 'not being annoying' and fell within some of the technical boundaries of what is considered a good alert for emergency situation (137). This theme concerned how the staff group perceived the technical sound itself. There is some research which discusses the effectiveness of alerts in clinical information systems or prescribing systems, (138) but there is little or no empirical data within the literature which relates to the effectiveness of specific audio alerts in pop-up information systems. The participants in this study identified that the key to effective alerts is the ability to be presented with an alert and place enough importance, emphasis or priority on the alert to encourage them to act (A3,14). It is also important that the noise is perceived as 'not annoying', which was the case in this study (A1, 1-3). The sound deployed

in this study was unique within the hospital dispensary. It was described as ‘different to anything else’ and was an alert which made participants think they had to act (A1,1-3).

The Effect of the Alert on Adherence to Policy (A2)

It was clear that an audio alert played a part in an improved adherence to policy (OAR) (**Table 5.2**), but it is not clear why this was the case, and what contributing factors facilitated this change in behaviour. The importance associated with the sound, and the fact that it was a home-grown change may have contributed to an improvement in adherence to policy; a concept that is explored later in this chapter. The audio alert used in this study would alert for only 4% of the medicines included in the study, as well as any individual medicine scanned more than once. It appears from participants responses in this study (A2,5) that an infrequently heard sound is more effective that one which alarms on a regular basis which runs the risk of being ignored; a less frequent alert has more meaning than a regularly alarming alert. In reality, the frequency of audio alerts will relate directly to the prevalence of falsified, expired or recalled medicines within that country, or the compliance in staff scanning the medicines. An increase in the occurrence of an audio alert may increase the likelihood of an alert being ignored. Conversely, an audio alert which sounds very infrequently carry's the risk that the staff member is unaware of its significance. Therefore, there are different issues associated with alerts of different frequencies.

Humans are naturally inquisitive. In recent years, we have become more and more familiar with smartphones and have been conditioned to

react with them when they alert. Perhaps this smart-phone mediated change of behaviour has augmented our inquisitive nature relating to sounds. When a phone makes a noise, it can be difficult to ignore the message or alert. It is in our human nature, now more than ever to deal with that noise. It is postulated that this has passed from our personal life to our working lives, resulting in audio alerts being more effective than ever at attracting attention and therefore improving staff adherence to policy. This point explains that modern culture of frequently if not instantly or incessantly checking one's phones has conditioned the general public even further to associate a vibration or a beep with a positive outcome, information that someone is thinking of us and wanting to contact us. Perhaps this behaviour makes those with smartphones more alert to audio alerts. As the majority of the users in this study were below the age of 50, it is likely that they have regularly used smartphones in the past.

Participants identified the concept of perceived sophistication in these interviews and explained that;

> "*The first time I used it, it didn't feel so sophisticated. It seemed strange that an audio alert can make a system more sophisticated, but that's what I thought" [P6]*.

In reality, this technology with an audio alert was identical to the technology without an alert. The audio alteration was the only change. Therefore, the concept of sophistication appears to be associated with the additional audio sound.

Too many competing sounds are likely to confuse the user within the environment however innovative methods such as vibrating scanners, keyboards or mouse could be used to alleviate this issue. Therefore, audio alerts should be reserved for the most important alerts in a given working environment.

Auto-Piloting (A3)

The quotes (A3,10-12) [P5&6] represent the opinion of the group as a whole and correlates with the quantitative ODR which improved as a result of this audio intervention; as described in **Table 5.2**. It appears that the sound reduces the risk of auto-piloting by adding priority to the pop-up alert and reduces the risk of alert fatigue, an argument which is aligned with improved authentication and detection rates from the previous chapter (**Table 5.2**). As seen in chapter five, sound adds priority to an alert, especially in a repetitive working environment and it can have positive and negative effects on the individuals and the group as a whole.

Positive individual autopilot

There was a consensus that the audio alert caused auto-piloting streamlined the verification process and improved efficiency. The participants explained that the audio alert allowed them to scan medicines quickly without the need to take time to read onscreen messages. The quantitative data in chapter five has made it clear that the introduction of an audio alert has made a, significant difference to the detection rate of the technology and therefore the net patient benefit is augmented by this 'active' alert.

Negative individual auto-piloting

Without a sound alert, a pop-up alone could result in a medicine generating a pop up and still being missed, the pop-up being automatically closed due to pop-up alert fatigue (139) or misinterpreting information resulting in poor quality medicines avoiding quarantine. Despite the ease of using the technology and the fact that the audio alert allows the user to work more efficiently while providing a safety net for auto-piloting, relying on the audio alert could cause complacency and over-reliance on an audio alert with little notice taken to the product itself or the associated on-screen reminders or pop-ups. This reliance behaviour may increase the risk of the operator not looking at the screen and further facilitate a behaviour of ignoring pop-ups alerts which do not have an audio alert or some kind of 'active' element. By allowing this behaviour to develop, it may negatively impact the behaviour of operators when using not only medicines authentication technology but also other health information technologies. Within this thesis, passive alerts were more likely to be ignored than their active counterparts, i.e. a sound alert (137). If passive alert information is routinely missed, as seen in previous chapters, then managers should consider permitting auto-pilot behaviour for the sake of efficiency in the process. Some may argue that audio alerts facilitate negative auto-pilot behaviour. However, when the primary outcomes, i.e. OAR, TDR, and ADR are compared between the study with and without an audio alert, it is clear that audio alerts have an overall positive impact in this context

Team auto-piloting

Depending on the personality of the operator (in a general sense), their level of confidence, level of experience or time in the role they may feel embarrassed or reluctant to seek help. The participants explained that audio alerts which attract the attention of surrounding staff, snapping surrounding staff out of autopilot dispensing behaviour and prompting them to help their colleagues. This facilitates learning and creates a non-confrontational avenue for assisting staff with tasks which they find difficult.

6.5.2: Point of Care Alert Appearance and Characteristics (B)

Coloured Pop-Ups (B1)

Throughout chapters three to five there was quantitative and qualitative evidence that staff members looked primarily at the colour of the pop-up and not the information contained within. In chapter five, there were two pop-up alert types, an amber and a red warning pop-up box which both generated an audio alert in chapter five but not in chapter three. There were two types of similar amber alerts (**Figure 5.5**), one which required product quarantine (potentially falsified medicine) and one which almost exclusively did not (authenticated here). The identification of medicines which produced an "Already authenticated here" alert was common in both studies and resulted in frequent and correct pop-up closing. However, as it was the same colour as the pop up which required quarantine, it resulted in many potentially falsified medicines avoiding quarantine, which demonstrated a difference in operational detection of 29% (**Table 5.7)** between the authenticated elsewhere (falsified) and the

red pop-ups (cumulative from chapter three and chapter five data). It was possible that the action of closing down pop-ups facilitated a sense of alert fatigue and sent staff further into auto-pilot mode for closing amber pop-ups generally. There was confusion between the two amber alerts because the operators looked at the pop-up colour and not the information on screen this resulted in medicines requiring quarantine being mistaken for those already dispensed on-site (129). This confusion worsened the 'alert fatigue' issue.

Point of Care Alert Characteristics (B2)

The "computer calendar alert', which is a pop-up alert which generated a sound to remind the user that they have an upcoming meeting in 15 minutes, was mentioned in the interviews and was believed to be an excellent example of an alert for many reasons. It is associated with an established technology company i.e. the computer manufacturer and had a sense of sophistication due to the presence of a sound with a pop up which appears on screen. Furthermore, the information is accurate (as the data is retrieved from user entered calendar information), the pop-up does not contain much text and is not a frequent repetition of the same message i.e. most commonly a new message for a new meeting. Therefore, the message is different every time; this provides a case for alerts which are kept up to date and occasionally changed in appearance. Furthermore, the calendar alert system is sophisticated, and the alert is active. Also, the alert is prioritised by the user as it is a message that they have inputted. The expectation to act in response to the alert is optional. Furthermore, by accepting a meeting invite you have already agreed and prepared yourself

for the alert and are therefore already accepting of its alert. An alert which is not pre-planned, like an alert to identify a medicine as being falsified or an out of range fridge alert can be stressful as the staff member is in no way prepared for this alert.

The staff referred to old-style pharmacy medication recording systems and explained that the alerts on these systems were often old, out of date and unreliable. By comparison, the alerts for the MAT examined in this thesis were modern, and accurate which were well received amongst the staff. Reliability and sophistication seem to be key. Staff also identified other noises in the department as important factors when considering audio alerts in the environment. Staff also suggested vibrating keyboards and handheld scanners to decrease the chance of missing a medicine which required quarantine. Simple messages were preferred, with the frequency of an alert playing an important role in how well staff adhered to the alert. It is hypothesised that the effectiveness of an alert relates to the priority placed upon it, and also the personality type of the user that is dealing with the alert. Their willingness to raise an alarm coupled with their level of experience and ability to prioritise will affect the net success of an alert.

6.5.3: Learning and Peer Influence (C)

Protocols (C1)

The study by Carthy et al. (140) explained that protocols are common in the healthcare environment, but due to their volume, many are often ignored out of the necessity of time-saving. If protocols are often ignored or go unused and only form part of a tick box exercise, then resources

should not continue to spent on these tools and instead, invest in alternative methods of education or procedure communication should be considered. The concept that protocols are ignored or undervalued is echoed throughout many of the interviews, e.g. C1,2 [P3]

"*Who likes reading protocols, SOPs but they're one of those things that have to be done"*.

Protocols are useful for putting clear rules in place, but from the participant's responses they do not appear to be a constructive way of educating staff. Everyone learns in different ways and the use of protocols alone are not the answer. Some staff explained that repetition was the best way to learn this new process. Therefore, this supports the argument that technology piloting before widespread roll-out is beneficial in reducing the risk of poor quality medicines being missed due to ongoing learning or teething issues.

It was observed that the length of time using the MAT technology didn't necessarily improve adherence to policy as authentication rates did not change between the first two-week pilot and the last eight weeks (stage one chapter three). Instead, it is theorised that time to reflect upon the technology is more useful than the time physically using the technology. There was time to reflect on the data collection period during chapter three and chapter five. This time to reflect has possibly facilitated a much greater effect on adherence to policy due to positive behavioural change that is not rushed or forced upon the staff which results in a more mediated diffusion of knowledge amongst the staff.

Discussed in the previous chapter, JKK or building quality from within ties in with Shojania's concept that 'home-grown' alerts or changes to HIT may be more effective than those imposed on the operators regarding adherence to protocol. As one participant stated

> "*I suppose if you've suggested something you think it's going to work and, yeah, you're probably more likely to make it work, aren't you"* [P5]
>
> or
>
> "*Maybe they felt more part of that change. They felt they wanted to be part of it rather than something that's going on and they didn't need to be a part of it*" [P6].

As the staff came up with the idea of how to improve this technology this seemed to have an effect. Not only did this effect the intended process for improvement (the quarantine process) but also overall technology compliance i.e. OAR improvement of 17.2% (15.2-19.3% 90% CI) $p<0.05$ (**Table 5.2**). Furthermore, at the end of the eight-week study in chapter five, all of the participants could explain that the inclusion of a sound was their own idea. Therefore, home-grown HIT alerts not only have a positive impact on the adherence to the specific alert but adherence to the wider technology within the environment that the home-grown improvement was made.

Despite the obvious quantitative gains seen in the previous chapter, there are concerns that successful home-grown HIT alerts in one organisation's site may not be accepted on another. This thesis identified a number of examples where cross-site workers explained that they

perceived other sites as being different in the way they work. It was explained by staff that what works for a district general hospital without a robot, for example, may not work for a larger hospital with a robot. Beyond this concept there are cultural, regional and team dynamic differences across sites which may influence adoption behaviour. Although entirely possible there is no concrete evidence, either way to say that a technology developed on site A wouldn't work on site B. It is possibly a competitive difference between staff on two different sites where one believes that their work is more difficult than another and therefore such a system would not be suitable for a more complicated working context.

Errors (C2)

In chapter three and five the staff explained that they never intentionally dispensed a medicine requiring authentication without first scanning it. The staff used a workaround which involved using a pen to place a cross through the 2D data matrix to ensure the same medicine was not scanned twice. Although this was effective, inventive, and helped when dealing with part dispensed packs, it would not be advisable long term. Although this reduces the need to scan medicine packets which have already been decommissioned, which is permitted under FMD legislation, it prohibits future verifications.

Peer Influence (C3)

As mentioned previously the addition of a sound impacted individual behaviour, but the external team were also affected by the presence of an audio alert. The team influence or peer pressure to

quarantine products may have been subconscious. When the alarm sounded, it may have created a fear of being considered by one's peers as one who doesn't appropriately act upon alerts. The influence of the surrounding team (similar to the Hawthorne effect) may have created a peer influence situation, therefore, facilitating the quarantine or justification for not quarantining medicines. Also, feeding into the theme of individual and team auto-piloting, this sound raised awareness to staff in the close vicinity, that someone has detected a dangerous medicine. Raising awareness, facilitated the identification of staff members which may have been struggling to remember the quarantine policy and encouraged more competent staff to step in at the right time. Therefore, an audio alert facilitates the raising of awareness of staff to their peers' activity.

6.5.4: Impact of the Technology (D)

On the Individual (D1)

Some participants said that when the technology was no longer being used they missed it, despite being initially overwhelmed by the new work process. Missing the sound shows that authentication in the workplace can work effectively even if it is at first a little overwhelming. Part-time staff have less exposure to alerts and the responses from part time participants demonstrated that it takes them longer to adjust to new systems. Infrequent alerts and noting using the technology regularly are a risk as it takes them longer to learn new systems than their full-time counterparts. The issue of part-time staff failing to authenticate, could be negated by more intense training for this group, or more frequent

revalidation as they pose a risk group for dispensing medicines without authentication. This is likely due to the infrequent nature of the alerts in this study (4% of all serialised medicines produced an alert). Therefore, the chances of a part-time staff member coming across a warning alert was reduced and therefore, so too was their chance of knowing how to respond in practice. As the WHO explains that up to 1% of medicines in the legal supply chain, are falsified and the majority of medicines are due for serialisation in the EU in 2019, it is possible that the rate of alerts will be similar in reality to the percentage seen in this study.

On the Workforce (D2)

There was a perception by the workforce as a group that this HIT impacted them. In relation to the workforce dispensing Controlled Drugs (CD's), they explained that CD's located in the separate CD room were missed due to proximity to technology terminal. To mitigate the chance of authentication non-compliance, scanning terminals could be located in every dispensing workflow, i.e. every room where dispensing and checking takes place. Furthermore, in busy departments, there may be a requirement for multiple authentications stations within the same room or on the same checking bench.

6.5.5: Technology Performance Issues (E)

During chapter five, the rate of offline issues was 4.67% (**Table 5.8**), and the qualitative interviews identify that this rate caused considerable disruption and was described as being annoying and disruptive. Chapter three, on the other hand, identified offline issues at a

rate of 0.44% (Chapter five, **Table 9.0**) and went almost absolutely unnoticed with no mention of it in the Delphi method study in chapter four. Perhaps this 0.44% mark could be used as a proxy for success in live medicine authentication across Europe in 2019; with 4.67% representing an unacceptable incidence of offline scans. Although the EU FMD states that the response rate limit should be 300 ms, it does not refer to offline issues, which can be caused by issues within the hospital, pharmacy or the central database which was largely the case in these studies.

6.5.6: Effective HIT Alerts

This chapter has identified concepts that appear to aid compliance to point-of-care alerts in the healthcare information technology sector which has given rise to the following schematic for effective HIT alerts (**Figure 6.0**).

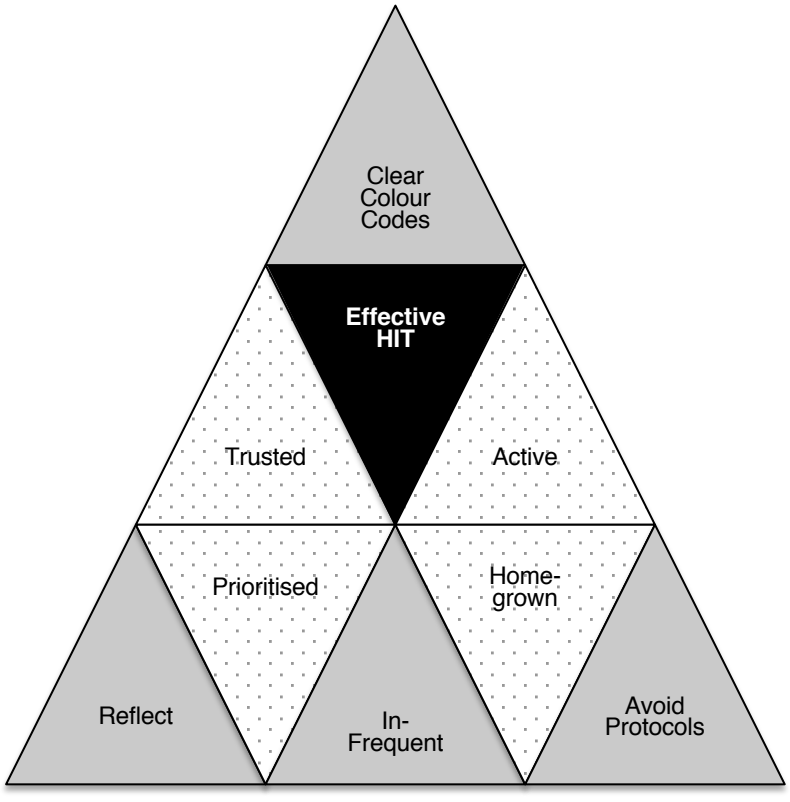


Figure 6.0: Considerations for effective HIT alerts.

Factors were identified by the staff to improve HIT alerts. The most important of which are identified in **Figure 6.0** and are summarised further below.

Active: Quantitative and qualitative results from chapter five and the study by Shojania et. al. (118) show that movement away from passive pop-up alerts and towards more active HIT point of care alerts may be an appropriate move. Active alerts that have, either a sound (for the most important alerts), a field in a HIT pop-up where data needs to be documented before progressing forward or some other 'Active alert' may be useful. Considering the effectiveness and suitability of active alerts is important if we are to combat the patient safety issue of auto-piloting and alert fatigue during pop-up alerting; an issue which may become more frequent as healthcare information technology becomes more commonplace. It is expected that other active alerts such as vibrating handheld hardware, e.g. scanner, mouse or keyboards are also likely to bring about advantages especially in noisy environments where multiple audio alerts may be confusing.

Trusted: The second attribute which has appeared to be important is the element of trust, this is connected to the perceived level of sophistication, which if high can associate positive connotations to the effectiveness of the HIT but also the reliability of the information being presented. It was clear that out of date information or large volumes of information which is repeated too often is often ignored and facilitates the issue of alert fatigue. Trust is easily lost. Maintaining trust in a technology information

technology relies on a system which has adequate resources to maintain and update its content.

Home-grown: Another principle raised during both quantitative and qualitative studies was the concept that building change from within an organisation is an effective way to gain user buy-in. The JKK model used in Toyota has been an effective well-documented approach which relates to the effectiveness of encouraging staff suggested changes to work process. Throughout this thesis, it is clear that developing a technology and being a part of the change is much more inviting for a staff member than following the direction to fulfil the requests of a manager. It is clear from this study that the staff knew it was their idea and as a result, they were more compliant, beyond the intended task (quarantine) but as part of the bigger process of medicine authentication which improved between chapter three and chapter five.

Prioritised: An effective alert is one which is prioritised by the staff responsible for adhering to it. The user benefits from understanding the context as to why this alert is important, and if staff see value in an alert, they are more likely to prioritise it. The value may be a reduction in the risk of dispensing a poor-quality medicine, streamlining of a process or the facilitation of an existing task. Education and training helps users to prioritise, and this is best served through the avoidance of long and wielding protocols. Instead, more interactive and memorable education and training methods are likely to be most effective.

6.6: Conclusion

The qualitative interviews with healthcare professionals in this study have identified a number of findings specific to the context of medicines authentication and have suggested some concepts or theories which are more general. The findings from this chapter are likely to relate to any technical staff working in a healthcare environment using computer alerts, staff working on a production line relying on alerts to detect poor quality products or in some cases may be relevant to customs inspection officials at international boarders, or airport security staff relying on alerts to identify unpermitted substances in passenger possession.

The introduction of an active alert such as an audio alert was not only effective at improving the detection and quarantine rate, but due to the home-grown nature of the alert, its benefits reached beyond the detection and quarantine process to an overall improved rate of medicines authentication; moving closer to FMD compliance and increased patient safety. There were a number of risks identified in this study which included workarounds (e.g. crossing through the 2D matrix to render it unreadable), part-time staff and end of day working. All of which may affect adherence to policy. Arguably the greatest concern to MAT commissioners should be the high prevalence of offline issues. The results of this study have demonstrated that a 4.67% offline rate can cause significant delays in the safe provision of medicines. According to the FMD, (18-19) in offline scenarios, the pharmacist must decide on whether or not to supply the medicine without prior verification. The pharmacist may feel pressured and awkward in this situation. There is a chance that a

pharmacist will supply a recalled or expired medicine without prior product verification. Thus far there is no information to help pharmacists understand their legal liability regarding this situation.

The ironies of automation, by Bainbridge in 1983 (141) states that despite the marvels of technology, it is often labour intensive, and more so if not constructed effectively. Until alerts are designed, based on rigorous studies which measure the effectiveness of individual interventions, it is unlikely that hospitals will reap the full benefits of HIT alerting. The considerations contained within the schematic for effective HIT alerts' (**Figure 6.0**) are worth considering when designing alerts for medicines authentication technologies, electronic prescribing systems, patient medication records and screening or identification systems in other industries. An effective alert benefits from being active, trusted, prioritised and where at all possible be home-grown or have elements of such. Having covered hospital digital drug screening in the previous chapters, chapter seven involves the creation of a digital drug screening app and assesses its potential use in the detection of falsified medicines. A convenience sample survey was conducted to learn about people's thoughts and opinions on this matter and are explored in the online medicine purchasing context in chapter seven.

7.0: Digital Medicine Screening with a Mobile Phone App: The Online Medicine Purchasing Context

7.1: Introduction

The previous chapters investigated the effectiveness of the FMD mandated, medicine authentication technology approach. To recap, this is a digital drug screening process which will be carried out by European organisations with a license to supply medicines. A healthcare professional supplying a medicine will be responsible for the scanning of a 2D barcode printed onto the outer carton of a medicine packet. The information contained within this 2D barcode will then be sent to a national database (NMVS) and cross-checked against a list of known legitimate product codes, as described in **Figure 7.0**. The healthcare professional performing this scan will be informed if the scanned medicine has been recalled, expired, stolen, or falsified. Previous chapters focused on hospital pharmacy and how this digital screening approach could be implemented and improved within the hospital sector. An unexplored area of research is how this same digital drug screening method can be converted into a mobile app to allow patients to verify that their medicine is from a legitimate source, and how would such an approach be accepted by consumers. This would be useful for patients buying medicines from unreliable sources in LMIC's and online. These apps could also provide information regarding how to safely and legally obtain medicines as well as providing drug specific advice for patients. Healthcare costs are rising internationally, with Great Britain's National Health System (NHS) spending increasing from 3.3% in 1960 (of GDP)

to 9.9% in 2015 (142). Medicine verification could help to streamline healthcare services in the UK. For patients, an app would allow them to learn more about their medicines and verify the legitimacy of the medication they purchase. This would be especially useful for medicines bought online, which is a growing trend. However, there are many concerns relating to healthcare providers and pharmaceutical companies accessing patient verification data. There are issues around data governance, and rights of the individual versus the commercial needs of the pharmaceutical company or healthcare provider. This is supported by a report from Mckinsey and company, which identifies ‘ A few caveats’ to the use of big data in healthcare, and state that ‘ Privacy issues will continue to be a major concern’ (143).

Turkey was one of the first countries to introduce medicine serialisation. Turkey also introduced a government app which allows patients to verify their own medicines. This app has been downloaded between 100 and 500 thousand times (144). The Turkish example demonstrates that it is possible for an app to connect to a national database or to a pharmaceutical company’s database of known legitimate codes. The FMD contains restrictions, such that, data generated by the FMD can only be used by competent authorities for falsified medicine investigations, pharmacovigilance, and pharmacoepidemiology purposes. Although it is not possible for a company to connect directly into the NMVS for the purpose of patient led verification, this could be performed by a competent authority, which might include a government organisation, University department, or hospital. However, there is the potential for a

private company owned app to connect directly into the manufacturers database of legitimate codes. This would allow a patient to scan a 2D barcode on a drug package and check the unique identifier against the manufacturers list of legitimate codes as demonstrated in **Figure 7.0**.

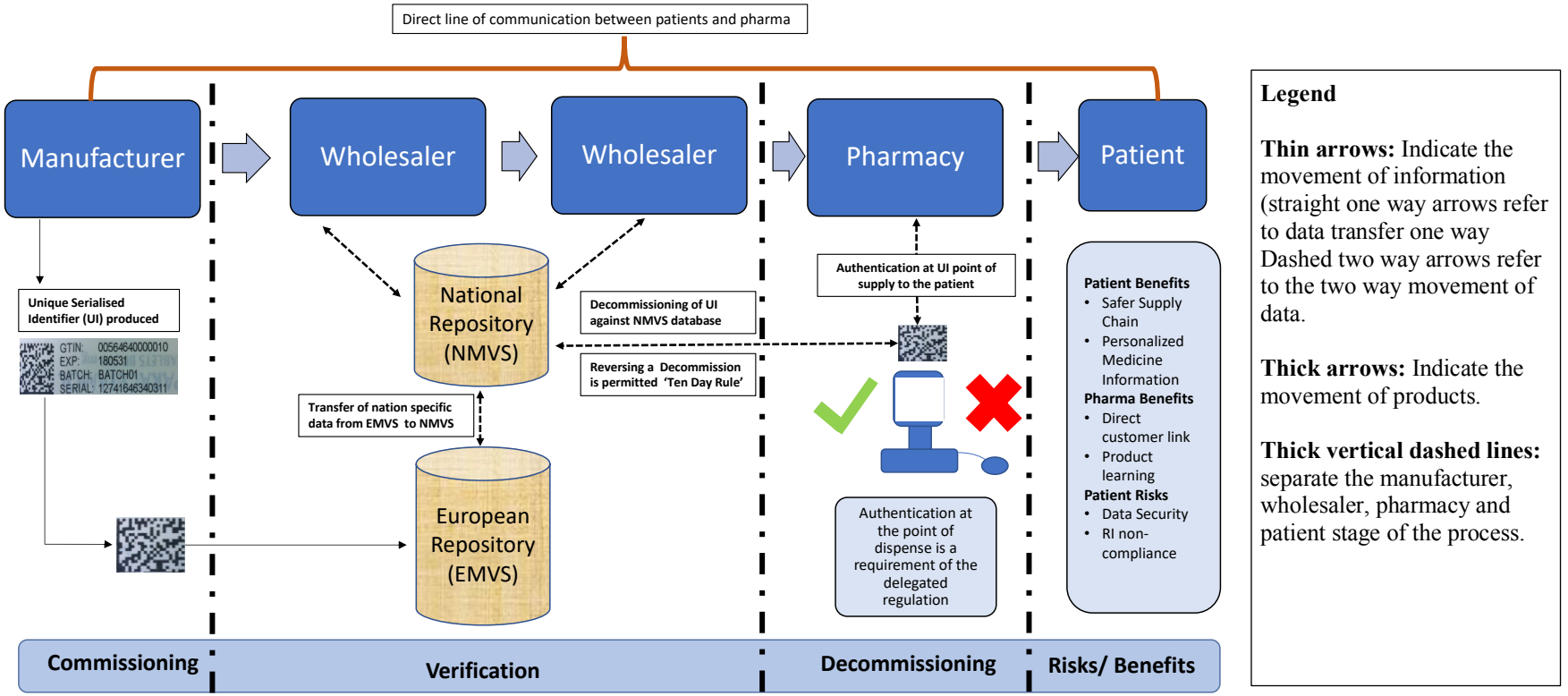


Figure 7.0: A diagram demonstrating the flow of medicines and data as part of the FMD; including a communication path between manufacturers and patients (a copy of Figure 1.1).

A medicine verification app for patients, if widely used, has the potential to generate a large quantity of data including drug names, strengths, quantity, and the geolocation where the medicine is scanned. This data could be of value to healthcare providers and pharmaceutical companies as it provides information on where medicines are being used and by whom. Similarly, the data generated from an app could help government organisations understand where medicines are being purchased and who is purchasing them. An app may also be a useful tool to send alerts when medicines are recalled, target patients on certain medicines with healthcare advice, or send reminders about medicine related check-up.

7.1.1: Purchasing Medicines Online

The problem of falsified and counterfeit medicines is most common in low and middle-income countries (LMIC's) and online sales in high income countries (HIC's). Therefore, the apps mentioned previously are likely to be most useful within these areas. This chapter will focus on how an app could be used within the context of buying all classifications of medicine online.

Patients are changing the way that they purchase medicine. From 1999 to 2003 in the US there was an increase in online sales of prescription drugs from $160 million to $3.2 billion (145). The behaviour associated with purchasing medicine online is likely to increase as internet access increases. In the UK in 2017, 90% of UK households had internet access, an increase from 57% in 2006 (146). 73% of adults had internet access

"on the go" using a mobile phone or smartphone (146). This availability to internet access has also influenced the rate at which goods and services are bought online; 77% of adults bought goods or services online, up from 53% in 2008 (146).

Consumer behaviour research on the topic of online medicine purchasing is scarce. This lack of research is surprising considering the rise of internet purchasing, the effect of poor quality medicines on health, (147) and the risks associated with buying potent medicines on the web (148-149). Online medicine sellers 'overshadow the nature and risks of the actual products they sell', making online medicine sales even more concerning (150). Consumers pay discounted prices (150) for medicines of all legal categories (Prescription only pharmacy, and general sales list medicines) which have resulted in a number of high profile deaths such as a 24 year old young girl that died after buying slimming pills online, (147) the death of a medical school student buying weight loss medicine online (151), or the death of the 22 year old due to an overdose of medicines bought online to treat period pain (152). Consumer behaviour relating to the purchase of counterfeit designer products is well researched but research into the behaviour, and incentives for buying falsified medicine is not (154).

There has not been any research relating to mobile digital screening of medicines and limited research conducted which explores the behaviour of consumers who purchase medicines online. Research to date falls into three broad categories. The first relates to surveys where participants volunteer responses which, although interesting, often extract

data from small samples and on a local scale. Although they look at why patients purchase medicines online, the majority of studies, like Fittler et al. in 2012 (154) are quite basic and focus on a small group of patients (hospital inpatients) in specific countries (Hungary). The second type of study, such as that conducted by Orizio et al. (2009) (150) looks at the legality of online pharmacies based on criteria such as the identification of a legitimate address and whether or not a prescription is required for the purchase of medicines. This type of study flags-up non-registered pharmacies but does not cover the behaviour or attitudes associated with the activity. The final type of study by Cicero et al. (2012) used fake medicines adverts to attract patients who could then be surveyed (155). This survey was an example of an online medicine purchasing survey and went some way to answer questions relating to participant decisions to buy tramadol online; participants buying tramadol online were at a higher risk of adverse events than those obtaining the drug from a doctor and pharmacist. Once the subject clicked on the website, a message then explained that the website visited was fake and was planted by the researcher. The purchaser was then asked to complete online surveys. The data collected related to one drug, which generated results specific to one population sub-type. Therefore, further research is required to understand if the incentives identified by Cicero are applicable for other medicines purchased online. Other questions include what participants understand about the safe and legal supply of medicines and if an app to verify the legitimacy of a product bought online would be helpful.

7.2: Aims

1. To gain an exploratory understanding of the following issues

    - The motivations of participants to buy medicines online.
    - The knowledge of participants in relation to safe and legal medicine supply.
    - Participant opinion on the potential of mobile phone apps to verify the status of a medicine.
    - Participants views on sharing their personal data and data obtained from medicine verification.

2. To identify potential areas for future research

7.3: Methodology

An exploratory research approach was taken. The recruitment approach was intended for scale and breadth. This study followed the Middleton et al (156-157) framework and used a convenience snowballing sampling method, via social media such as LinkedIn, Twitter, and Facebook . An online mixed method survey was used. This survey included quantitative and qualitative questions including a video of an avatar providing education regarding the safe purchase of medicine online and how to verify a medicine purchased online (**Appendix 7.0**). As this was an exploratory study, the inclusion criteria in this study were broad and included English speaking internet users as described in the Middleton et al. framework (157).

Convenience sampling has its advantages. It is useful tool for exploratory research in areas where there is little or no existing literature. It also has advantages in situations where resources are limited. Convenience sampling can generate large amounts of data in a short space of time. It can also be useful for identifying hard to reach populations,

such as those that have purchased medicines online (158). The disadvantages are, that it is difficult to remove bias from the sample, even with large sample sizes. When using a convenience sample it is not possible to infer that the results represent the wider population, due to participant selection bias (159). There is also a greater chance of outliers (participants that do not belong in the dataset) in the sample due to inherent sampling methodology (160). Considering the early nature of this research area, and the limited resources available, the recruitment of a randomised representative sample was not possible. Therefore, the results in this chapter are described to facilitate general learning and the identification of future hypotheses.

7.4: Methods

An anonymous online mixed methods survey, with a randomised response recording, was written by the lead researcher and piloted with members of the research team and acquaintances of the lead researcher to identify improvements to the survey questions. (**Appendix 8.0**). An invite to this survey was posted by Keele University, the University of Oxford and the lead researcher's professional, LinkedIn, Twitter, and personal Facebook accounts. Participants read information regarding the study and ticked a box consenting to being involved in the study. Participants were asked to answer a selection of open and closed questions relating to the study aims (**Appendix 8.0**). Participants were also asked to view a video of a mobile app being used to authenticate medicines. The video showed the scanning of a 2D barcode on a medicine packet followed by a response, to identify if the medicine was recalled, expired, falsified or

authentic (safe to use). The video also contained a video recording of someone completing in-app questions relating to the purchase of medicines online. The questions within the app regarded whether the medicine was bought online, which website it was bought from, whether the website purchased from contained a common EU logo (a picture of the common logo was provided), if a prescription was requested or if medical questions were asked. The app then produced drug information for the patient to read followed by an avatar which explained the risks of buying medicines online, and how to check if an online pharmacy website was legitimate using the EU FMD common logo. The video also contained an avatar which was used to demonstrate how to verify a medicine using the app. This survey was live for four weeks (12/2/18 until 12/3/18). The survey was posted and re-posted through a variety of social media sites by the lead researcher, his contacts, and their connections. Payments were not made to participants.

7.5: Ethical Approvals

This study was classified as research according to NIHR guideline's and as such required ethical approvals which can be found in Appendix 4.0, p 292.

7.6: Results

7.6.1: Sample Demographics

This study attracted 227 respondents of which 219 consented to the study. The largest group of participants were aged between 25 and 39 (n=139) **(Table 7.0).** There were more female than male respondents

(Table 7.0) and participants originating from 22 countries. The majority (n=195) of respondents originated from the UK, Ireland, the United States, and Australia **(Table 7.0).** A variety of employment status's and levels of educational were covered by the respondents. The majority (n=198) of respondents were full time or part time employed. Full time students (n=14) and the unemployed (n=7) were also represented (**Table 7.0).** 77 respondents had health insurance, 128 lived in a country which provided free healthcare, and 14 participants didn't have health insurance and didn't live in a country that provided free healthcare; therefore, they paid for their own health care as required **(Table 7.0**.).

Table 7.0: Demographics of chapter seven participants

Total (N)	Consented (N)	Age Group (N)(%)	Gender (N)(%)	Country of Residence (N)(%)	Ethnic Origin (N)(%)	Employment Status (N)(%)	Highest Level of Education (N)(%)	Healthcare Provision (N)(%)
227	219	30-39 (85)(39)	M (81)(37)	UK (135)(62)	White British (112)(51)	Full Time (168)(77)	Undergraduate Degree (97)(44)	Free Healthcare (128)(58%)
					White Irish (68)(31)			
		25-29 (54)(25)	F (136)(62)	Ireland (56)(26)	Other White Background (19)(8)	Part Time (30)(14)	Postgraduate Degree (70)(32)	Health Insurance (77)(35)
					Mixed White and Asian (3)(1)			
		40-49 (38)(18)		United States (10)(5)	Other ethnic background (2)(1)	Unemployed (7)(3)	Secondary School (27)(12)	Neither, Self-Provision (14)(6)
					Information refused (3)(1)			
		50-59 (21)(10)		Other European (6)(3)	Black or Black British Caribbean (2)(1)	Full time Student (14)(6)	PhD (17)(7)	
		19-24 (64)(6)		Australia (4)(2)	Black or Black British-African (4)(2)		Other (6)(3)	
		60-69 (5)(2)		Hong Kong (2)(1)	Asian or Asian British - Indian (4)(2)		Primary School (2)(1)	
		70-79 (1)(1)		South Africa (2)(1)	Other mixed Background (1)(1)			

		90-100 (1)(1)		United Arab Emirates (2)(1)	Asian or Asian British– Pakistani (1)(1)			
				Canada (1)(1)				
				Ethiopia (1)(1)				
				Isle of Man (1)(1)				

7.6.2: Awareness of Illegal Online Pharmacies

Two of the respondents correctly identified that between 91 and 100% of online pharmacies were operating illegally; the remaining 169 participants were surprised to hear that up to 97% of online pharmacies were operating illegally.

7.6.3: The Safe and Legal Supply of Medicines

The majority (n=217) of respondents knew what a prescription was. The majority could identify doctors, pharmacists, dentists, opticians and nurses, or a mixture of all five as the main professionals legally permitted to supply a prescription, however 21 participants didn't know or were not sure and 67 participants chose 'other'. The majority of the respondents mentioned either pharmacists, dentists, the NHS, or doctors as being the professionals permitted to supply drugs with 34 choosing other. The majority (n=215) of respondents knew that all medicines did not require a prescription.

Respondents gave many legitimate reasons why prescriptions were needed, for example;

'*Monitor drug usage*, … *ensure correct medications are given*' [#60],

'*To legally obtain drugs*' [#18]

To prevent risk to patients [#109]

'*To allow you to legally obtain medicines'* [#68].

7.6.4: Purchasing Medicines Online

Respondents were asked whether or not they would consider buying medicines online, and 132 said that they would. In another question, participants were asked, on a scale of 1-10 how likely they were to buy medicines online and the majority (112 of 219 participants) chose either one or two (Mean response of 4.35), demonstrating that they were unlikely to buy online **(Figure 7.1)**. 51 participants explained that they had bought medicines online.

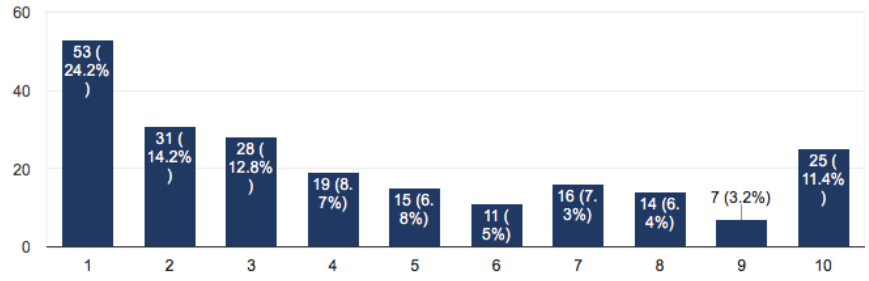


Figure 7.1: The likelihood of respondents to buy medicines online with one representing unlikely and 10 representing highly likely.

A free-text option from the survey allowed participants to identify the medicine, or medicine type that they purchased online. A summarised list of medicines, is included in **Table 7.1.** These medicines are separated into the three most common UK legal class's, Prescription Only Medicines (POM), Pharmacy only medicines (P), and General Sales List (GSL). Some medicine classes differ based on the strength, quantity, formulation, and country they are purchased in. Therefore, the medicines mentioned in this study are listed according to the most frequent class for each product in the UK.

Table 7.1: Medicines purchased by respondents.

POM	P	P, or POM	GSL	Supplements
Antibiotics	Orlistat	Acne Cream	Bio-Freeze	Chondroitin
Antimalarials	Minoxidil	Antacid	Silcocks base	Glucosamine
Blood pressure medication	Fungal nail infection ointment	Emergency Contraceptives	First Aid Kit supplies	Natural Desiccated thyroid supplement
Contraceptives	Paracetamol based cough medicine	Nappy Rash cream	Paediatric nasal salt water	Garlic Supplements
Valium (Diazepam)	Antihistamines	Fluconazole	Deep heat	Co-enzyme
Galfer (Ferrous Fumarate)	Calpol (Paracetamol suspension)	Hair Loss medications		Herbal Ointments
Inhalers		Sildenafil		Omega 3
Modafinil		Steroid Cream		
Ventolin		Weight loss tablets		
Retin-A (Tretinoin) cream		Voltarol (Diclonec)		

There were a number of reasons why the participants in this study purchased their medicines online. Participants selected from a predetermined list of motivations for buying medicine online;

1. Physically unable to get to a pharmacy,
2. I have to wait too long to get an appointment from my doctor,
3. Was embarrassed about my condition,
4. Buying medicine online is more convenient,
5. Buying medicine online is cheaper.

The two most prevalent reasons for participants, buying medicines online were that is was more convenient (n=20), and that buying medicine online is cheaper (n=24). There was a free text space in this question where 17

other responses were offered. These responses mainly focussed on access issues;

> '*The specific medication that is most useful for my condition is not available in my country'* [#82]

Or due to their GP not being willing to supply the medicine:

> '*Dr will only prescribe two weeks of treatment, despite chronic condition*' [#35].

The point relating to a GP's unwillingness to supply was mentioned in this study a second time where the same participant stated;

> '*I was desperate as local GP will only prescribe very short-term treatment in low doses*' [#35].

One participant also stated that they bought medicines online because of

> 'GMC *stupid self-prescribing rules, and stupid pharmacists*',

The same participant explained further in this study

> '*I can't self ******* prescribe because of GMC*' [#148].

Of the 51 respondents that bought medicines online 18 of those purchases were for prescription only medicines (by UK classification). Of the 18 participants, 14 were not asked for a prescription. From this cohort there were nine people that were not asked for a prescription or asked medical questions when buying prescription only medicines. One participant described his consultation as:

> '*A rip-off of a fake consultation*' [#148].

There were some side-effects experienced by the participants that bought medicines online; these included:

1. '*Increased heart rate'* [#169],

2.‘*Actually caused lack of side effects which made me think cream was fake,’*

3. [#30] ‘*Headaches, sweating, anxiety’* [#224], and ‘*Fatty stools and incontinence*’ [#224].

Despite buying and taking medicines bought online, 12 participants explained that they were concerned that the medicine they purchased could be fake. From the cohort of 51 participants there were a variety of methods used to identify whether or not the website or medicine was legitimate. These methods are categorised as themes, represented as quotes, and are summarised in **(Table 7.2).**

Table 7.2: Themes emerging from methods used to check the legitimacy of an online pharmacy website [participant number #].

No Checks
None, just had bought from it (online site) many times before but not medicines [#17]
The product is manufactured from the same supplier that a prescription could have given me. They are cheaper, and a prescription is not required in this case. So, the safety of the website is not a factor to me. [#46]
The bio freeze company was the merchant of record [#98]
I assumed it was safe [#167]
None, because the product works (this is bad I know) [#169]
Word of mouth reviews [#225]
Reading reviews
By looking for recommendations on online forums [#30]
I consulted with a person I knew who was involved with the retailer [#99]
Asked friends where they purchased from [#224]
Using a well-known or reputable website or company
It was the website of a pharmacy I used to shop when I lived there [#37]
Bought through an online pharmacy that is linked to a high street pharmacy. They asked a variety of health-related questions [#156]
Bought from Amazon, reliable source [#220]
Other checking methods
Google search or company registration number check [#51]

I conducted extensive research to ensure that the website was genuine, authentic, regulated and safe [#82]
Research the company I was buying from. Check their address on Google earth, recognise the name of the company, ensure site was safe (Https) and not a redirect [#87]
Checked their registration from link to gov (government) website [#198]
Register with regulator GMP approved [#206]

7.6.5: Apps for Medicine Verification

Participants were asked how they checked the medicine they received to make sure it was of good quality. The responses varied from not checking, checking the packaging, or stating that the products were from a well-known manufacturer or company. Some participants also explained that they used taste or smell as a marker for quality;

> '*I have had used Ventolin for 20+ years and would know the difference between real or fake,* either *by its effect or taste*' [#161], '*It smelled fine, tested a small amount of the cream on the watch strap clasp side of my wrist, didn't break out in a rash, so it seemed safe enough*' [#220].

The key methods for identifying whether or not a medicine was legitimate was by checking the packaging, relying on purchasing from a legitimate seller, or none at all (**Table 7.3**)

Table 7.3: The measures taken to identify if the medicine received was safe to use.

None
None, had before [#118]
Checked the packaging and seals
The medication had my details, the packaging was sealed and secure and had the drug name on the packaging with no errors, spelling mistakes [#195]
I look at the covering [#139]
Checked it was all sealed and not tampered with [#215]
Came in sealed RX bottle [#135]
Checked the packaging and seals were in tact [#50]
Testing
Tried a very small amount [#35]
It smelled fine. Tested a small amount of the cream on the watch strap clasp side of my wrist. Didn't break out in a rash, so it seemed safe enough [#220]
None, I have had used Ventolin for 20+ years and would know the difference between real or fake. Either by its effect or taste [#161]
Trial and error. Matched effects with those of known active agent [#224]
Source assessment
Most of the research I undertook was to ensure that the medication was safe including contacted the manufacturing lab and receiving information about the FDA approval they have and the standards they adhere to [#82]
Collected medication from the high street branch of the online pharmacy [#156]
Collected in store from pharmacy [#159]
The remedies were from a well-known manufacturer or company [#37]
Checked the online pharmacy was registered [#198]
No idea. I wouldn't buy tablets over the Internet. Maybe creams. I wouldn't know how to ensure they were safe? Only on judgment of website, where they are based [#13]

The majority of respondents (n=152) explained that they would use an app to verify their medicines, 44 participants responded maybe and 23 said they wouldn't;

'*Busy life means that going to the doctors can be time consuming and appointments aren't always available- if you could get a*

prescription online and be sure that the medicine was safe and legitimate it would save a lot of time' [#163].

And another participant explained that an app;

'*Helps to identify counterfeit medication especially when more online pharmacies/online doctors (Babylon/ push doctors) are providing services'* [#7].

On a scale of 1-10 the majority identified the app as being more useful than not (**Figure 7.2**) and there was an appetite for the app as a whole, including education as well as a verification function (**Table 7.2**).

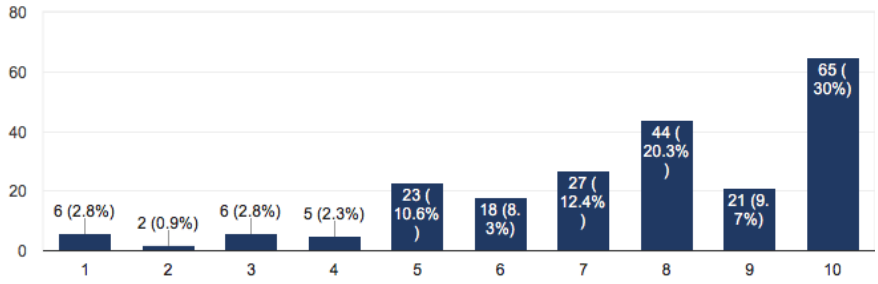


Figure 7.2: A rating scale identifying the participants opinion regarding how useful the app is with one representing not useful and 10 representing very useful.

191 participants said they would scan their medicines when they received them and 19 said they wouldn't, with the remainder providing a number of caveats as to why they may or may not use it. The participants in this study identified a number of ways to support or encourage the use of a medicine verification app which are displayed in **Table 7.4**.

Table 7.4: Summary of concepts to support or encourage the use of an app to verify medicines in order of preference.

Promotion and Support
'The best way to encourage its use would be to get a big community pharmacy to endorse it like boots. However, would they? Not so sure if we consider they may well be advertising themselves out of a profession' [#65]
'*Promoted by all doctors that issue prescriptions and supported by pharmacies when medicines are collected'* [#138]
'App being free plus supported by government [#96]
Cost
'Free access' [#138]
Education and Awareness
'*More exposure on the risks of fake medicine'* [#12]
'*Might work well if promoted, but people can't be bothered to use it and don't know the importance'* [#217]
Data Security
'*It'll only work if people are buying online. But people may be afraid of getting in trouble if their app data is shared'* [#111]

The potential of using an app to verify the legitimacy of a medical product was put to this cohort. 122 did not see any barriers to using an app like this, 16 were not concerned about the risks of buying medicines online, and 14 didn't have time to scan their medicines, 10 did not have access to a good internet connection, and 52 respondents gave other unique answers. Participants also identified a number of factors which may negatively affect this type of technology (**Table 7.5**).

Table 7.5: Qualitative descriptive quotes of why an app like this may not work well.

Age
If older people need to get the app they may struggle to download it or people may forget to use is [#123]
Lack of awareness or concern
People may not be bothered they are buying fake drugs [#12]
…If you are inclined to buy medicine online maybe you aren't concerned about safety [#79]
Trust and Reliability
People may not trust it [#15]

It may not work well if it is deemed as unreliable [#52]
International Issues
May not cover internationally produced drugs, my online medicine comes from India [#35]
Being in a different country and not knowing the language or where stuff is made [#39]
Requirement for further information
I would need to know more about the parameters of its overall use [#41]
Can you get in trouble, legally if you buy from places like this? Would using the app and reporting a fraudulent drug make the end user culpable in some way? I'm not sure I would ever buy anything that would require an app like this [#50]

7.6.6: Data Sharing

The participants view on data sharing were sought during this survey. This involves the scanning of a two-dimensional barcode on their medicine pack to verify the legitimacy of their product. Participants were shown a video of an app being used to verify a medicine and were asked who they were most likely to share their personal and medicine verification data with (**Figure 7.3**).

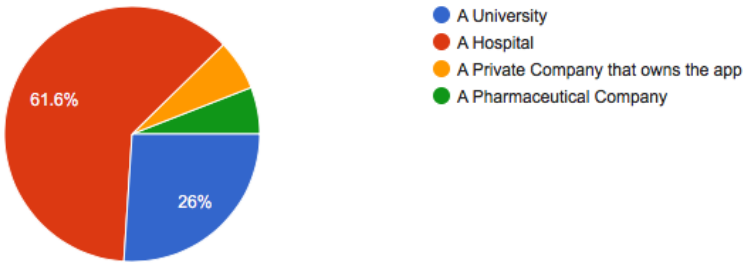


Figure 7.3: Graph representing who the respondent would be most likely to share their personal data, drug details and scanning location (verification data) with.

61.6% of participants would prefer to share their data with a hospital, 26% would prefer a University, 6.3% would prefer a private company that owns the app and 5.9% would prefer a pharma company. A

number of key quotes were extracted which support the theme that a sub-population of the sample were untrusting when it comes to data sharing. One participant asked;

> '*How accurate can this app be and why should people trust this app*?' [#146].

Another participant questioned the security and privacy behind the app.

> '*Confidence that the data you are scanning is not being cultivated by some out of sight online entity that is now keeping track of every drug I am prescribed*'
>
> '*Super shady*' [#154].

One participant summarised the views of the data conscious by saying

> '*I would definitely not use it if it was collecting personal data about me*' [#82].

7.7: Discussion

7.7.1: Sample Population and Awareness

The most common respondents of this survey were well educated, white, British or Irish, between the ages of 25 and 39, in full time employment (**Table 7.0**). Over 70% of respondents (n=169) were surprised that 97% of online pharmacies were operating illegally (161). This result identified a poor level of awareness relating to the extent of the illegal online pharmacy problem amongst a largely well-educated cohort with access to online sources of information. Participants under the age of 19 were eligible for this study but there were no responses from those in this age bracket. This is possibly due to the recruitment methods used. LinkedIn, Twitter, and Facebook were used to disseminate this research

survey, however the University of Chicago identify that the most popular social media forums for teenagers are snapchat and Instagram (162). Snapchat and Instagram were not used as they are primarily photography based social media and would not be as suitable for survey dissemination. Furthermore, teenagers can be difficult to reach, engage with, and convince to participate in research. This may be due to their stage of life and the stresses associated with being a teenager e.g. exam stress, physical appearance, and friends (163). A larger more randomised sample would be required to understand if this is also the case amongst a randomized sample.

7.7.2: Safe and Legal Supply of Medicines

Many respondents gave different answers to describe why a prescription was needed. These responses included reasons such as safety, legality, drug addiction, and to prevent suicidal overdose with safety the top reason identified. These responses correspond to recent deaths associated with associated with purchasing medicines online, which include the young girl buying slimming pills, which had a toxic ingredient such as dinitrophenol (164). Another example was the case of another young person self-medicating with medicine purchased online who died from an overdose (152).

Obtaining medicines without a prescription and associated healthcare professional advice can have risks that the general public may not be aware of. These risks include interactions with other medicines and incorrect dosing (165). Buying POM medicines online without a

prescription carry even further risks which relate to the legitimacy and quality of the product purchased.

7.7.3: Buying Medicines Online

132 respondents stated that they would consider buying medicines online and 51 participants had purchased medicines online. The highest-ranking reasons for buying medicines online were convenience (n=20) and cost (n=24). In the wider online purchasing context, cost and convenience are top reasons for buying products online (166-167). In a study by Cicero et al. (155) convenience scored low on motivations for buying Tramadol online, which does not correlate with our findings. However, this may be due to a reason specifically related to tramadol. The top two reasons for buying tramadol online in the Cicero study were 1. Difficulty in finding a doctor to prescribe the opioid medicine, and 2. Doctor will not prescribe enough; again, this may be a factor that is unique to buying potentially addictive drugs purchasing online. The survey conducted in this chapter identified one example of a potentially addictive medicine being purchased online. This example related to diazepam and in that case, the participant that bought the diazepam online also explained that he was motivated to do so because his doctor refused to supply enough of the medicine.

> *I was desperate as local GP will only prescribe very short-term treatment in low doses*' [#35].

In this case the participant went on to buy this medicine online form a website that did not require an online consultation or a prescription. This

is a case of a patient bypassing the GP to obtain medicines, and this behaviour puts patients at risk.

There was an isolated participant in this study who stated that GMC self-prescribing rules had encouraged him to buy medicines online

'*I can't self ******* prescribe because of GMC*' [#148].

This is an example of a healthcare professional knowingly bypassing a system and acting against the regulations of his professional body with disregard for legal medicine supply. Buying medicine online from a reputable source is not a problem if the website the prescriber is purchasing from is legitimate, however in this case the website used appears to be illegitimate, as the prescriber explains that the online consultation he experienced was a '*Rip off, of a fake consultation*' [#148].

Eight of the 51 participants that purchased medicines online thought that the medicines they were buying were or may have been fake, counterfeit or of poor quality and a further seven thought they might have been. This highlights conflicting behaviour. Despite having concerns about fake medicines consumers still take risks. For instance, when a participant was asked what steps they took to check the website was legitimate;

'*None, because the product works (this is bad I know)*' [#169].

From the participant results in this study it is not possible to understand how prevalent risk taking is amongst those buying medicines online and what factors override the risks of buying a potentially falsified medicine. Regarding participants that are aware of the risks of buying medicine online, and still purchase, public health campaigns that highlight risk may

not be effective, and educational campaigns that describe how to verify the legitimacy of a website might be more suitable.

Products like the contraceptive pill, the morning after pill, Valium, steroid creams, inhalers, hair loss medicines, sildenafil, weight loss medicines, pain relief, blood pressure medicine, and antibiotics were all described as being purchased online (**Table 7.1**). There is scope for information to be supplied to a patient at the point of purchase. Information could be presented in an app or video, which aids consumers within the European Union to verify an online pharmacy website. Many respondents took no precautions when buying these medicines online and others stated online reviews and reputable sources, as methods of checking the legitimacy of a website (**Table 7.2**). The data from this cohort suggest that there is great variation in this cohort. There are those that are aware of the risks, but chose to ignore them, and those that have developed their own methods for verifying the legitimacy of an online pharmacy website. Furthermore, only one person mentioned the EU common logo verification process introduced by the FMD. A mobile app would be able to provide information regarding a government website checking process and may also be able to provide other useful information at the point of verification. Future research is required to understand the level of knowledge surrounding the EU FMD common logo website verification process. In terms of product quality, consumers relied on what was perceived to be a reliable website, and often checked packaging as their only means of verifying quality (**Table 7.3**). The implications of this

practice, are that a well-designed website or well copied packaging may not correspond to a legitimate website or legitimate product.

7.7.4: Mobile App

191 of respondents reported that they would be prepared to scan their medicines using an app like the one demonstrated as part of the online survey. 122 stated there were no barriers to using the app and have identified that the public would be willing to use an app if it was available. They considered this to be a useful app which was simple to operate. One participant responded to the question 'What do you think needs to be in place to support or encourage you to use an app like this?' with;

"*Not much I would love to use it if it was available*" [#33].

In summary the respondents placed a big emphasis on the need for an app like this to be endorsed or supported by the NHS, government, or established pharmaceutical companies, with more weight being put on Hospitals and Universities due to increased levels of trust (168). Respondents also stated that the app would benefit from an advertising and marketing campaign which would involve online and community pharmacies as well as doctor's surgery's. According to participants the barriers which face this type of app relate to concerns regarding trust, the ability of the elderly to use the app and Wi-Fi availability. A participant was also concerned that there would be a risk the 2D codes could be faked (**Table 7.5**). Another important point made by a participant was that those buying medicine online may not realise there is a problem and therefore the problem first needs to be publicised before introducing a solution.

Other reasons surrounding why the participants may not use the proposed app, include lack of awareness, ignorance to the issue of falsified medicines, trust or reliability in the app, or fear of retribution from buying a medicine online; according to survey responses. Although there were a variety of interesting responses there were no recurring themes through the responses as to why an app like this may not work. The only exception to this relates to data privacy and security which is discussion in the following section.

Some participants relied on the reliability of a website or the reputation of a company as measures of drug safety. Other participants checked the packaging; the majority made no attempt to make sure the medicine they received was safe. Some individuals used crude physical tests as a measure of quality, such as the taste of an inhaler, the smell of a product, or the effectiveness of a cream tried on a small patch of skin initially. Although the mobile app method is not an absolute solution for patients as it is possible for a 2D barcode to be copied, it is a safer and more reliable way of testing the legitimacy of a product, than testing based on taste or lack of efficacy.

According to Bessell et al. (169), consumers who buy medicinal products online;

"*Have insufficient access to information and advice at the point of ordering and on delivery to make informed decisions about their safe and appropriate use*"(169). This applies equally to medicines they buy online. Results from this study identify that a mobile app that both provides relevant educational information and verifies the legitimacy of a

product may be a suitable solution to the issue of "*insufficient access information and advice at the point of delivery*". As online doctors' appointments and online pharmacy orders become more commonplace (170), the need for digital screening tools to verify the status of a medicine and provide tailored medicine counselling could for some patients, help to maintain trust, and safety in the absence of the healthcare professional interaction.

7.7.5: Data Sharing

Some participants identified data control as an issue with the medicine verification app. The reliability and trustworthiness of such apps and the data they produce was also questioned. This is echoed in the results relating to whom the respondent would be most comfortable sharing personal data, and medicine verification data (geolocation and drug details) with. Respondents preferred to share their medicine verification data with hospitals (n=135) and universities (n=57) rather than pharmaceutical companies (n=13) or a private company owning the app (n=14) (**Figure 7.5**). One participant mentioned

> '*confidence that the data you are scanning is not being cultivated by some out of sight online entity that is now keeping track of every drug I am prescribed*' and described it as '*Super shady*' [#154].

This ties in with data presented earlier in this chapter which explained that participants largely suggested Hospitals and healthcare professionals should promote the app, in contrast to a smaller sample that suggested legitimate pharmaceutical companies should promote the app. Therefore, this cohort is likely to have most trust in an app under the control of a

Hospital or a University when compared to a pharmaceutical company. Considering comments relating to data sharing, it is of no surprise that hospitals are the most trusted, as they already hold personal data for patients. This corroborates with data from the UK information commissioner's office (ICO) which states that 'UK citizens are more likely to trust public bodies than private companies or organisations regarding holding or sharing their personal information'. The ICO further corroborates the findings in this study by identifying that three in five, (61%) of the public say they have trust and confidence in the NHS or local GP to store and use their personal information (168). Whereas only one fifth of the UK public (20%) have trust and confidence in companies and organisations storing their personal information (168). The idea of access to verification data has been mentioned in the FMD. In article 39 of the FMD it is stated that 'The member state shall grant access to the repository…. (database holding verification information) to competent authorities of that member state'(18). Article 39 then states that this access should be for the purposes of supervision and investigation of episodes of falsification, for reimbursement, pharmacovigilance or pharmacoepidemiology studies. Article 39 does not mention the use of this data by pharmaceutical companies and therefore the sentiment of article 39 is reflected by the respondents of this survey as they state a preference for sharing data with a hospital or university ahead of a pharmaceutical company. This is corroborated by the UK ICO data. Considering this, there are still a proportion of respondents from this cohort that would be happy to share their data (verification or health) with

a pharmaceutical company, and it would be interesting to understand what motivates them to do so. Is it a financial incentive, is it a lack of awareness, perceived high levels of security, or some other factors?

The EU horizon 2020 programme puts Responsible Research and Innovation (RRI) at the centre of research. 'RRI implies that societal actors (researchers, citizens, policymakers, business, third sector organisations, etc.) work together during the whole research and innovation process in order to better align both the process and its outcomes with the values, needs and expectations of society' (171). There is commercial potential for patient verification of medicines but it is important that any innovation in the area of mobile medicine verification is an example of RRI. Regarding the development of these apps, it will be important to consult with patients to understand what they want, to educate them regarding how their data might be used, or where it might be stored.

7.8: Weakness in the System and Drivers for Change

There are a number of obstacles to patient led medicine verification. This relates to database access. If this app was linked to the EU hub or a national hub, patients could verify their own medicines. This would allow the public to verify all prescription only medicines using an app. Currently this is not the case and would require government permissions. Alternatively, this app could be connected to the databases of pharmaceutical companies. This would mean that this service would only be available for some medicines. Both approaches could be funded by pharma if the medicine verification service also provided medicine

information at the point of authentication or other useful non-commercial material. Government could permit a hospital or university to connect apps to this database to allow patient verification. The app will require advertisement and members of the public may require incentivising to use the app. There are also concerns that mobile devises connected to national and European databases could compromise the security of pharmaceutical serialisation data.

7.9: Limitations

A limitation of this survey was the absence of a section for participants to record feedback relating to the survey; which may have been useful for example, to understand why some participants did not consent to the survey. Also, there were no stratification questions which identified whether or not the participant was medically or scientifically qualified.

8.0: Summary of Conclusions

The SF medicine problem affects many industrial sectors and countries and poses a global health risk. SF medicine is an issue that affects healthcare, involving community pharmacy, hospitals and commercial companies throughout LIMIC's and HIC's. The prevalence of medicines fraud is increasing on a yearly basis throughout both legitimate and illegitimate supply chains, (172) and it is clear that SF medicines are more of a problem in LMIC's than HIC's (173). Substandard and falsified medicines are in essence a 'Wicked Problem as defined by Grint (2005) (174). A 'Wicked Problem' cannot be solved by bureaucratic and technical solutions. It requires adaptive leadership and policy making and the convening of new conversations amongst groups who can help progress. Such groups include healthcare professionals, and the general public.

This problem extends beyond the individual who fails to receive the correct dose of active ingredient and can affect society as a whole by exposing populations to low doses of antibiotics resulting in multidrug resistant bacteria. In the current age of international travel, these microorganisms travel across continents. Therefore, antibiotic resistant issues caused by substandard and falsified medicines (SF) in one country can easily affect another.

There is much work to be done in LMIC's to identify medicines, establish SF medicine 'hotspots' and provide public health initiatives to educate local populations. Although not explored in this thesis, successful leadership is likely to play an important role in the fight against falsified

medicines. This leadership involves understanding financial and non-financial incentives to collaborate, and bringing relevant policy makers, researchers, and government agencies together to pool resources and intelligence. The impact of falsified medicines regulations on pharmacy practice, may require pharmacists to alter the way they work to comply with the incoming legislation (175).

8.1: The Prevalence of Falsified and Counterfeit Medicines

There are a number of organisations that conduct medicine quality studies which in part aim to understand the prevalence of SF medicines in circulation. These organisations include NGO's such as WHO, and University academic groups that use laboratory techniques to assess the quality of medicines, largely antimalarial medicines in LMIC's. Chapter one has identified that these approaches are often cumbersome, expensive, require a trained laboratory assistant, and are often destructive, i.e. the process of analysing the medicine renders it unusable. This is an important factor in LMIC's as medicines are not always easily accessible. Although not ideal these methods are often the only options available in LMIC's. Due to a lack of funding, and the necessary infrastructure required to carry out these medicine quality studies on a larger scale, they often yield small sample sizes. The number of medicines assessed in these studies are often too small to draw any significant conclusions. In 2017, the WHO released a report which identified the prevalence of SF medicines to be 10% in LMIC's. The true prevalence of SF medicines in LMIC's will remain unknown until significant samples are gathered. It is anticipated that the process of gathering larger samples sizes required to represent the

medicine quality in a given area would be costlier, and labour intensive. The emergence of medicine serialisation regulations, manufacturer serialisation activity, and healthcare professional verification of medicines could be the solution to the issue of low sample numbers. This will only be possible in LMIC's that have widely available internet access and medicines that are serialised.

Medicine packs will be serialised with a 2D data matrix in Europe by February 2019 with a 2D data matrix and a unique identifier code in many regions around the world, e.g. EU, US, Brazil, China and Turkey. It may be possible for a healthcare professional or patient in Europe to scan this 2D data matrix with a smart phone and verify its legitimacy against the manufacturers database of known legitimate products as seen in **Figure 7.0**. If pharmaceutical companies fund the drug serialisation process in LMIC's as well as HIC's, the cost of verification to healthcare professionals and patients with a computer or mobile phone would be minimised. Although it is possible to copy a 2D data matrix of a product, once the copy of the 2D data matrix is scanned and verified against a database, the database would raise an alert to explain that this is a barcode that has been scanned elsewhere. This would trigger an investigation into both products to identify which was falsified, therefore this risk is somewhat mitigated. Verification is not destructive, it does not require intensive training and if performed by healthcare professionals and patients, it could generate a greater volume of medicine quality data than traditional laboratory-based techniques.

Chapter three and chapter five presented how the use of a digital screening technology resulted in thousands of medicines being screened for quality in a hospital over an eight-week period. This avenue would facilitate the systematic screening of medicines and would empower healthcare professionals, and potentially patients, to assess medicine quality in large numbers. The data generated from such a strategy could help health service payers to understand the true prevalence of falsified, recalled and expired medicines in a given region. Facilitating the mobilisation of healthcare professionals and patients through the provision of tools to verify the legitimacy of their products, if successful, would generate an enormous quantity of data relating to drug quality, suitable for inferring a prevalence of falsified medicines in a given region. This data could also be a valuable public health resource to target public health campaigns and could be used to inform national medicines regulatory authorities of SF medicine cases. Policy makers and government organisations could permit a University, Hospital, or government agency to connect into the UK NMVS with an app. Policy maker could be encouraged to use this medicine verification data, generated by healthcare professionals and patients, in a responsible way to understand more about the pharmaceutical supply chains in Europe and internationally. It is hoped that a UK government funded department or University group is established to analyse the data generated by medicines verification, and patient apps, and analyse that data to understand the true prevalence of falsified medicines within the legitimate NHS supply chain and purchased online from pharmacies claiming to be based in the UK.

8.2: Implementation of Serialisation Regulations

Serialised medicines are due to enter European pharmacies before February 9th 2019 in Europe. Other countries such as the US, Turkey, Brazil and China have already begun this process and further nations are following. Chapter two examined the impact of the FMD on hospital practice and identified a key feature of the FMD was the requirement to re-commission medicines which are decommissioned in error or require returning. It was established that this must be done within ten days of decommissioning, otherwise the medicine cannot be sold on to another organisation. This would have financial implications for hospitals and community pharmacies in the UK that are involved in wholesale dealing.

Chapter two also identified the effect that FMD regulations and associated drug screening technologies may have on pharmacy practice, in terms of where in the dispensing process to scan medicines. Decisions will have to be made by hospitals regarding where to scan their medicines and these decisions will be based on the services the hospital provides, the physical layout, and flow of medicines throughout the hospital. Some hospitals will find that their only solution is to scan all their medicines at the 'Goods-in' stage, while others will opt for medicines to be scanned at the 'Goods-out' stage, namely as medicines leave the pharmacy to be sent to a ward as ward stock or leave the dispensary to be sent to a ward for administration to a specific patient. Both options will satisfy the FMD regulations, however it is anticipated that the most secure method would be to scan medicines at 'goods-in', 'goods-out', and at the bedside as part of the scan4safety project which involves the scanning of a patient's wrist-

band, their drug chart, and then the drug to ensure the safe administration of medicine. This is likely to generate more value from the medicine scanning operation. Government organisations such as the MHRA, and NHS England could promote the value in using the FMD generated data to streamline purchasing and stock control within the NHS. It may also be useful for government agencies and relevant working groups produce and promote materials to outline a roadmap to FMD compliance for hospital and community pharmacy.

8.3: Digital Medicine Screening Technology

When looking at methods of identifying SF medicines it is difficult to avoid paying attention to incoming global supply chain regulations, such as those emerging in the US, Europe, Turkey, China, Brazil and Europe and beyond. These regulations look to use database cross checking and blockchain technology to support the identification of SF medicine. The NHS has often struggled with successful technology implementation projects and considering these previous failures, UK hospitals that are currently unprepared are also likely to struggle to reach FMD readiness by February 9th 2019.

If managed appropriately, the FMD and its associated serialisation and Digital Medicine Screening Technology (DMST) approach could be a success. DMST success can be measured against a number of parameters which include OAR, ODR, and ADR. When the DMST is rolled out these parameters will show that compliance is not initially absolute, as seen in chapter three. It is anticipated that the Response Rate (RR) of the Digital Medicine Screening Technologies (DMST's) will not be a limiting factor

however offline issues may pose a threat to medicine dispensing. In chapter three, offline errors made up 0.44% of scans. In chapter five they made up 4.67% of scans. It was only during chapter five that the offline errors were identified by staff as being problematic, and therefore a rate of 4.67% is an unacceptable level. When the DMST goes offline pharmacists will have to make a judgement call whether to dispense a medicine or ask the patient to call back until the DMST is back online, the frequency of this event will depend on the reliability of the national database (NMVS). This thesis suggests that in terms of OAR, checking staff are best suited to medicines verification in the dispensary, ahead of their dispenser colleagues. However, the margins were small and there were no statistically significant differences between both study groups in chapter three in terms of medicine detection (ODR). Therefore, if decommissioning of medicines at the dispensing stage works well from an operational standpoint, a decision to decommission at the dispensing stage could be justified. If introduced at the dispensing stage, PMR software could be configured to generate dispensing labels only if the medicines 2D barcode is scanned. This is likely to generate much improved authentication and detection rates. Each hospital pharmacy will have a different context and it is useful to consider this context when rolling out the FMD. Staff compliance to authentication, detection and quarantine processes has been shown to be an issue (Chapter five and chapter six) therefore any roll-out of a FMD verification system will require some form of staff monitoring. The greatest FMD related risk to UK pharmacies are offline issues associated with the national database. It

is suggested that the UK NMVO could mitigate the risk of this incoming technology through contractual obligations with NMVS providers. Payment for these NMVS database services should be performance based, and financial penalties should be in place for excessive periods of offline instances. Without these penalties, the NMVS providers have no incentive to deal quickly with offline issues.

Digital drug screening technologies do not require a skilled operator. However, they are only as good as the operator. It is unlikely that a technically accurate screening tool will translate into a 100% decommissioning or detection rate. During this thesis it is clear that human factors will play a key role in the rate of authentication (OAR), quarantine (ODR), and overall removal of recalled, falsified, and expired medicines from the hospital supply chain (ADR). It is important that hospitals do not assume that because a technical solution is in place that staff are appropriately identifying and quarantining products. In pharmacies, both community and hospital, dispensing errors and near misses are recorded and reviewed by management on a regular basis. The same should be done for OAR, and ODR through the monitoring of scanning data when compared to dispensing figures. (The same cannot be done for ADR as this would require knowing how many expired, recalled, and falsified medicines were in the system to begin with. Knowing this without removing them would be unethical) A national authentication and quarantine rate standard should be released and audits should be conducted to assess compliance to this standard.

8.4: Consensus Studies

This thesis suggests that consensus studies are useful tools which help a team to decide on the most suitable changes for their context. In the chapter four the consensus approach united staff in decisions and helped to identify changes which brought about positive change. In this thesis we saw that a consensus study was responsible for the addition of an audio alert to a DMST, at the point of identifying a medicine that required quarantine. This sound was largely responsible for the 13.5 % (**Table 5.2**) improvement in ODR and 30.1% (**Table 5.2**) improvement in ADR. This Delphi study identifies a number of other improvements for DMST's which include reviewing the colour of alert pop-ups, encouraging staff to act on warnings, and adding a mandatory 'action' taken step. If these improvements were implemented in isolation it may be possible to understand the effectiveness of each change, which would contribute to the literature on the effectiveness of HIT alerts. Policy makers should consider the effectiveness of consensus studies when implementing larger HIT projects. Results from this thesis identify that consensus studies bring teams together and improve compliance to change. Stakeholders regularly report that they are not considered enough during HIT change and that change is often pushed upon them (111). In order to alleviate this issue, it is recommended that during the implementation of large HIT projects, consensus studies are reported to the funder to evidence that the opinions of the stakeholders are being incorporated into project implementation plans.

8.5: The Effectiveness of HIT Alerts

When the quantitative results from chapter three and five are taken into consideration alongside the qualitative results in chapter six it becomes clear that there were a variety of factors that contributed to the improvement in authentication and detection rates in this thesis. The considerations contained within the schematic in **Figure 6.0** (repeated below) may help with the design and effectiveness of HIT alerts. The qualitative and quantitative results showed that the colour of the alert was important and affected how the user reacts. The confusion between amber and red alerts was referenced by participants in both studies (Chapters five and chapter six) and demonstrated the need for clearer alerts in busy healthcare environments. It was also evident that 'home-grown' ideas were easier to implement than those introduced by an external manager or consultant, which was supported by the results in this thesis, further supporting the consensus study method mentioned previously. Involving staff in consensus studies is similar to the JKK practice used by Toyota. JKK encourages staff to make improvements, through encouragement, staff feel empowered, which in turn results in more ideas and better change implementation and compliance. It was clear from qualitative interviews that the staff were aware that it was their idea to add the audio alert, and some participants went as far as to say that because it was their idea they were more willing to make it work. Beyond the micro process of medicine detection, it is possible that by involving the staff in the change it also affected wider compliance. In this case the staff suggested audio alert would only sound when a medicine which required quarantine was

scanned. The increase in authentication rates was not anticipated by both researcher and participating staff; this was confirmed in interviews. Using JKK principles to build in quality with ownership appears to not only to have motivated staff to be more complaint during the micro-process of correct medicine quarantine, but also had a positive impact on a meson-process i.e. overall technology compliance (authentication rates) (OAR).

Other factors which have contributed positively to an improved OAR, ODR, and ADR include the active element of the alert (audio alert) and the fact that the alert was not constantly alarming. As the alert was infrequent it reduced the likelihood of autopilot behaviour at the time of identifying that a medicine that required quarantine. It was clear from these interviews that Health Information Technology (HIT) alerts that are not trusted e.g. are not accurate, up to date, relevant, or lack sophistication are less likely to succeed than those which are. Protocols were identified as a poor method to educate HIT users and should be used less frequently. Instead a more interactive learning approach is preferred with the opportunity to reflect and re-try the HIT. Although there is a risk of staff becoming over reliant on the audio alert and ignoring pop-ups, this research identified that the OAR, ADR, and TDR all improved in the presence of an audio alert making it possibly the most effective method for identifying recalled, expired and potentially falsified medicines.

It was clear that an audio alert not only raised the awareness of the operator but also those surrounding them. This raised awareness which facilitated interaction with colleagues surrounding the DMST operator.

This interaction promoted help and education between staff members in relation to medicine quarantine. The interview data also suggests that the widespread use of smart phones which often 'Ping' and vibrate may have conditioned those who use them to be more curious to the outcome of a 'Ping' or vibrate.

Finally, from an operational perspective, decommissioning stations would be useful in multiple locations. Qualitative interviews in chapter six, show that movement between rooms for the purpose of decommissioning, disrupts the dispensing process, and increases the likelihood of medicine de-commissioning non-compliance. Therefore, the results from this study would recommend that there is at least one decommissioning facility in every room where medicines are dispensed e.g. controlled drugs rooms and extemporaneous drug rooms.

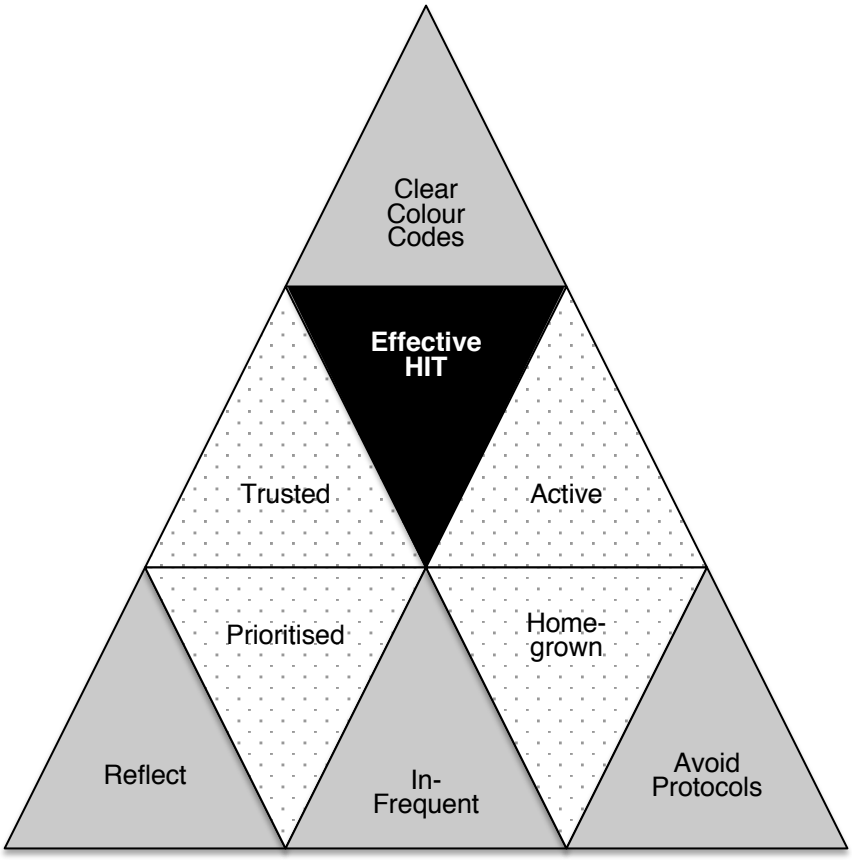


Figure 8.0: Considerations for effective HIT alerts (repeated figure 6.0 for reference)

This thesis demonstrates the advantages of involving staff in the change management process. As Shojania et al. (138) explains, home grown technology or change can be most effective. It would not be feasible for a technology company to create a different version of their HIT to suit every customer context. However, if technology companies provided a number of alert options such as different pop-up displays, different sounds, or vibrations this would allow the customer to conduct consensus studies with their staff on the best combination of settings for their environment. This would add an element of home grown change in a pragmatic way and encourage better HIT compliance.

8.6: Online Medicines and Mobile Digital Medicine Screening Technology

In today's society many consumers prioritise cost and convenience when buying products and according to the findings in this study this is also the case when purchasing pharmaceuticals online. The appetite for convenience drives up demand for medicines ordered online and although there are plenty of legitimate online pharmacies the vast majority are not. Chapter seven was conducted as exploratory research and aimed to generate hypothesis from the results to facilitate future research. The largely 'well educated' cohort from our sample had good knowledge regarding the safe and legal supply of medicines and took calculated risks when buying medicines online. Many purchased medicines online even though they were concerned they may be dangerous. It is unknown which reasons compelled participants to buy online despite their concerns of the associated risks. Further research might include repeating this survey with a randomised sample to encourage those from different backgrounds (such as different educational backgrounds or ages) to understand their behaviours in relation to the purchase of medicines online.

The app demonstrated in chapter seven, facilitated the safe supply of medicines from legitimate online sources through education, and had the ability to verify a product. In order for such an app to progress beyond the demo phase, such an app is likely to benefit from an awareness campaign backed by government organisations such as the NHS, and by healthcare professionals. Only one of the 51 respondents who bought medicines online eluded to the idea that they may have used the EU FMD common logo as a method of verifying legitimate online pharmacies;

'Checked their registration from link to gov (government) website' [#198]

More could to be done to educate the those buying medicines online about the risks of this practice and how to verify the legitimacy of online websites. Another contributing factor amongst this cohort was the confusion regarding what medicines required a prescription and which did not. There was confusion over who was legally permitted to write a prescription. This coupled with a poor level of education surrounding which medicines require a prescription leads to a sense of perceived safety. If a medicine is perceived to be safe, then it may be perceived that a prescription is not required, which may lead a patient to buy a prescription only medicine online without an online consultation or prescription.

Participants positively accepted an app for the verification of medicines and demonstrated more willingness to share their data with an hospital or university as opposed to a pharmaceutical company or other private company. This means that in this cohort, in order for an app of this description to be used and trusted it would require governance of a hospital or a university, with the former being the preferred option by participants in this study. Trust is an important factor to consider when discussing electronic commerce and it is likely that a relationship with a hospital or university would generate the trust required for a medicine's verification app like this to be successful (176).

Currently, at the point of receipt there is no systematic, cost-effective, and practical way for a patient to identify that a medicine

received is safe to use. Giving patients the ability to verify their own medicines may allow them to be involved in the battle against SF medicines. Through the empowerment of patients, we can potentially understand better the prevalence of substandard and falsified medicines, and the areas worst hit. In the future apps like the one demonstrated as part of the chapter seven survey, which contain avatar education, provide an opportunity to educate HIC and LMIC country populations to the risks of buying medicines from illegitimate sources at the point of receiving their medicines. If patients have the ability to verify medicines, this will be a concern for any pharmacies that purchases medicines from illegitimate sources. The reputational damage associated with a patient self-identifying a medicine as falsified may be enough to deter any community pharmacy from purchasing medicines from illegitimate sources.

The problem of SF medicines cannot be tackled by one industry or discipline alone. The problem is best solved through collaborative work between government, pharma, primary care, secondary care, medical researchers, social science researchers, and most importantly patients and consumers. The problem of SF medicines is indeed a 'wicked problem' (174). It is suggested that government bodies could allow a secure mobile phone app to connect to the UK NMVS. This will allow patients to verify their medicines against the list of known legitimate products. This tool will also help the MHRA to record which online pharmacies are being used, and whether or not the medicine received is from a legitimate source. It may be useful that these apps and the data they collect are kept under the control of a public body such as a University or NHS trust to maintain

data security. It may also be useful for this app to be supported by government agencies to promote usage by the general public and to maintain trust in the product.

Legitimate online pharmacies could educate patients regarding the process of verifying a legitimate website, this in turn will help to retain business for legitimate online pharmacies. It is recommended that legitimate online pharmacies provide education regarding how to verify an online pharmacy website using the EU FMD common logo, with interactive educational videos or avatars. It is anticipated that this education may raise awareness amongst those buying medicines online and systematically educate those involved in online medicine purchasing. This may add an extra level of sophistication and reliability to the legitimate online pharmacy.

9.0: Future Research

Further medicine verification pilots may be useful to understand how FMD medicine verification could be incorporated into the national scan for safety project. Another useful pilot may be the verification of medicines at the 'Goods-out' stage, as medicines leave pharmacy stores. Further pilots would provide an understanding of the obstacles facing these processes. Other future research relates to the financial implication of the FMD in terms of drug wastage and resources required to facilitate the implementation of the FMD safety features, i.e. the 2D data matrix and tamper proof seal. Government organisations overseeing FMD roll-out such as the MHRA, and department of health could consider the findings of this thesis when advising on the implementation of the FMD safety features across great British hospitals and community pharmacies.

Further research may include the assessment of the average OAR, ADR, ODR, RR, and frequency of offline periods nationally and internationally to investigate contexts where these rates are closest to perfection. From this data it may be possible to better understand what management techniques, or other contextual factors facilitate higher rates of technology compliance.

Future research may include questions such as, will the introduction of these technologies and the requirement to verify medicines slow down the delivery of medicines to patients? and what are the implications of product serialisation on SME pharmaceutical companies, and how will the FMD effect drug shortages (177). From the healthcare perspective there is much work to be conducted around supply chain

management in terms of how medicines move around hospitals, how to improve efficiency and how to better alter organisational behaviour to promote improved innovation adoption of technology to improve efficiency.

Future research may also include the trialling of different sounds to understand acceptable technical ranges for a certain technology in a particular context. Each of the parameters in **Figure 6.0** could also be tested individually to see if they improve compliance to HIT alerts in an effort to generate meaningful comparative data to inform the design of future HIT alerts.

Research in the area of online medicines purchasing requires further attention. This might include repeating the chapter seven survey with a randomised sample to encourage those from differing backgrounds and age groups to participate and to understand their behaviours in relation to the purchase of medicines online. It may also be worthwhile conducting a more randomised study which targets specific groups such as teenagers at school.

There was very little evidence to suggest that the cohort of participants in this study used the EU FMD logo to verify the legitimacy of the online website they used. This participant sample was not randomised, and therefore a future study which randomizes the sample would be useful to understand if the lack of awareness of the FMD common logo seen in this study is the case across the rest of Europe.

More research is required to understand the concept of 'perceived safety' identified in this cohort. Further research using qualitative

interviews would help to gain a deeper understanding of the behaviours associated with buying medicines online and how financial incentives might affect the willingness of participants to share data.

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Appendices

Appendix 1.0: Inclusion criteria and selection process for study medicines

The inclusion and exclusion criteria (**Figure 1.0**) facilitated the choice of a balanced cross-section of drugs in the study dispensary, ensuring that product groups with the highest level of medicine counterfeiting are included while also ensuring that medicines legislated by the FMD are investigated in this study.

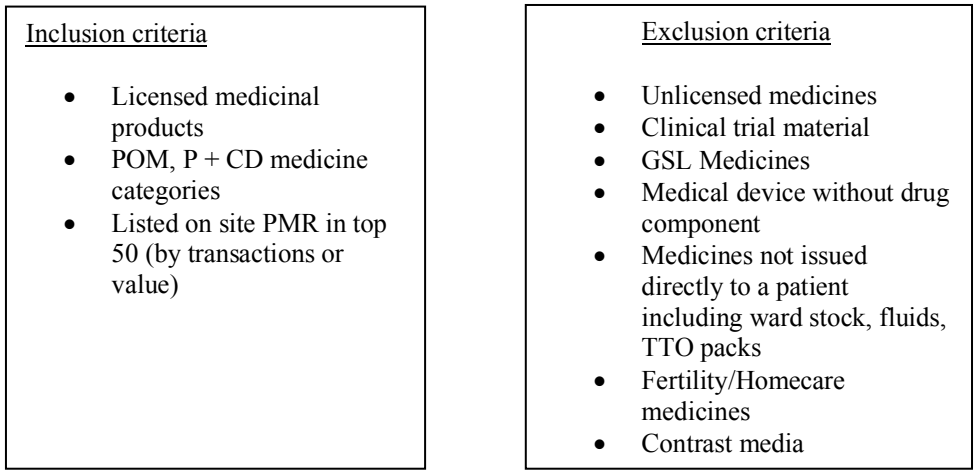


Figure 1.0: Inclusion and exclusion criteria for study medicines.

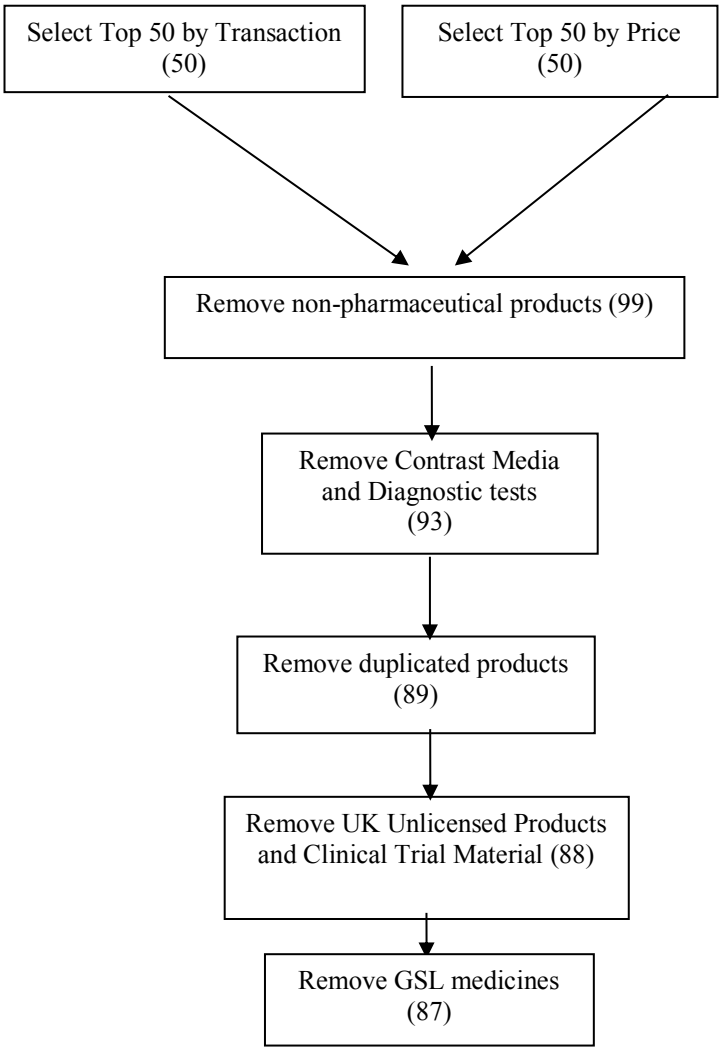


Figure 2.0: Decision tree for selection of portfolio of medicines.

In accordance with the FMD annexe one licensed POM medicines have been included in this study. An exception has been made for a small number of high volume medicinal products which are not POM. This exception facilitated the inclusion of some of the highest turnover drugs. Products such as clinical trial material and medical devices (without drug component) are not covered by the FMD and coincidentally do not fall

into either of the two top 50 categories. Contrast media has not been included in this study in accordance with the FMD (annex one). Products not containing medicines, such as clear dossette box containers, a common non-pharmaceutical product which appears on the hospital patient medication record (PMR) have been removed from the study. Both top 50 lists were checked for duplications, which included low molecular weight heparins and common intravenous fluids. General sales list medicines (GSL) e.g. Senna and unlicensed medicines such as Pentosan are removed from the study as neither are covered by the FMD.

Appendix 2.0: The optimisation of a medicines authentication system. A study protocol

The Impact of Audio on Counterfeit Medicines Detection

Protocol 001: Research Stage 1
Author: Bernard Naughton
IRAS Reference: 210334
R&D Reference: 12284
Research Ethics Committee Reference: ERP 2289

Protocol Version	Date
3.0	06/06/16

Funding: Keele University, Aegate Limited and the University of Oxford

Study Site: The Horton Hospital, Oxford University Hospitals NHS Foundation Trust.

Roles and Responsibilities:

Primary Investigator: Mr. Bernard Naughton (University of Keele, University of Oxford and Oxford University Hospitals).

Senior Tutors: Professor Stephen Chapman (Keele University), Dr. David Brindley (University of Oxford) and Professor Sue Dopson (University of Oxford).

Commercial Sponsor Representative: Mr. Paul Thomas (Aegate Ltd).

AHSN Representative: Dr. Lindsey Roberts.

OUHFT Representatives: Mrs. Emma Pullan and Mr. Bhulesh Vadher.

Pilot Sponsor: Keele University

The funding source provider had no role in the design of this study, execution of this study, data analysis or decision to publish.

A project steering group committee meeting took place on November 11th 2015 at the University of Oxford Said Business School. The following is a list of all attendees. Prof. Sue Dopson (Oxford), Prof. Stephen Chapman (Keele), Dr. David Brindley (Oxford), Dr. Nick Scott-Ram (AHSN), Dr Lindsey Roberts (AHSN), Mr. Bernard Naughton (Keele/Oxford/ OUHFT), Mark Di Simone (Aegate), Paul Thomas (Aegate), Emma Pullan (OUHFT), Bhulesh Vadher (OUHFT/AHSN) Cristiano Ressi di Cerviav (Aegate).

Apologies: Professor Sir John Bell (Oxford), Graham Smith (Aegate) and Professor Georg Hollander.

Ethics committee approval is granted for this project [1].

Background and Rationale:

Prevalence:

The prevalence of counterfeit medicines has risen internationally over the past number of years [2]. According to the Pharmaceutical Security Institute there were 2077 incidents in 2014, up from 196 in 2002 [3]. Although this may be due to improved security and detection methods, this statistic clearly identifies an increase in the incidence of pharmaceutical counterfeiting. Furthermore, it is currently estimated that 1% of medicines in the developed world, 30% in the developing world and 50% of online medicines are counterfeit [4].

European Law and the Falsified Medicines Directive (FMD)

There is a range of legislation relating to falsified medicines in Europe. Such legislation includes the Bollini law introduced in Italy in 2000,

which requires medicines to be tracked to the point of sale using two barcodes [5] and laws in Belgium and Greece, introduced in 2005 which have resulted in mass serialisation of drugs by manufacturers [5]. The FMD was introduced in 2011 by the European Union and aims to harmonise legislation across Europe to ensure the highest standards in medicines authentication. This FMD legislation can be summarised into six key points (**Table 1.0**).

Table 1.0: The key points arising from the FMD [5] [6]. The new FMD promotes non-invasive medicine verification and authentication.

1	Serial numbers and 2D barcodes are to be attached to medicinal products at manufacture
2	Over the counter medicines (unless deemed vulnerable) will not require authentication
3	All prescription only medicines (unless excluded via risk assessment) will require authentication
4	Tamper-evident seals will be required for all products
5	All European pharmacies will be affected by this directive
6	Manufacturers are responsible for the cost of the Medicines Authentication System

Importance of study:

By 2019, all member states must be fully compliant with the regulations set out in the FMD delegated acts; published in the first quarter of 2019. Implementation of this directive will be required 3 years from the date of

publication of the delegated acts and will require significant learning before the 2019 deadline [7][8].

The European Medicines Verification Organisation (EMVO) has recommended three national blueprint systems to provide verification services throughout Europe. These providers are Aegate Ltd, Arvato and Solidsoft Reply.

The introduction of MAS has proven to be a suitable option for medicines authentication in secondary care however some issues have been raised in terms of authentication and therefore detection rates. It is of vital importance to optimise the medicines authentication technology (MAT) in preparation for the 2019 deadline in order to facilitate a fluid transition. In Q3 2015 a service evaluation project was conducted by this research team to evaluate a medicines authentication system in an effort to understand the process, how it would affect hospital practice and to identify any issues that may influence its effective implementation.

It is critical to build on and improve the medicines authentication process and to establish best practice for medicine authentication in secondary care before the 2019 deadline [7][8].

Choice of comparators: A dispensary in a district general hospital, part of a larger NHS foundation UK trust UK hospital, with a standard medicines authentication system and the same site with the same system altered to create an audio sound to alert staff when a potentially unsafe medicine has been scanned.

Research hypothesis:

The inclusion of audio sounds triggered by the authentication of counterfeit or unsafe medicine improves the authentication and detection rate of counterfeit medicines

Null hypothesis:

The inclusion of an audio sound does not improve the authentication and detection of counterfeit medicines.

Primary objective:

To identify the authentication and detection rates of a counterfeit, recalled or expired medicines over an 8-week period with an audible sound notification and compare this to the identical scenario without an audible sound notification (service evaluation stage).

Secondary objectives:

To identify reasons for less than 100% authentication/detection rate(s).

To identify commonly un-detected medicines

MAT down time

MAT response time

To identify the incidence of false positives

Methods:

Study setting – A district general hospital that spans a wide range of medical and surgical wards with specialist treatment areas including Cancer, Renal, Coronary Care and Paediatrics.

Product identification:

A small unpublished audit of medicines was undertaken at the pilot site which identified a limited number of products containing the FMD

compliant 2D data matrix code (2D code) printed on the product by the manufacturer. This number was deemed insufficient to capture the data required for the study. Therefore, serialised adhesive 2D code labels must be created* (Appendix 1.0. Point 9), accompanied by a database (from this point onwards referred to as "the database") detailing data for each adhesive label. This database must be maintained by the site researcher under password protection and backed up on a weekly basis by the site researcher.

Researcher labelling procedure

2D code labels must be attached to selected products (Appendix 2); the barcode database must be updated to document the product name, form, strength and pack size of the labelled product.

To identify inclusion in the study a small purple label (Appendix 1.0, Point 6) must be placed beside the expiry date of each selected product line (Appendix 2.0).

2D codes must be placed on products using the following hierarchy:

1. Beside the expiry and batch number
2. On the opposite edge to the expiry and batch number
3. An area without text
4. In the rare circumstance that text is covered, this text must be repeated on at least one other location on the packet.

A single 2D barcode label was placed on the outer container of medicines that contained numerous medication vials.

[3]*Restrictions:*

[1]*Labels are kindly sponsored by Domino Ltd. and cut to size by Brackley Labels Ltd.*

Labels must be attached to all available products in each location on Monday and Wednesday between 7:00am and 14:00 every week. These criteria have proven to be appropriate in the pilot study.

96% of medicines labelled are to contain pre-programmed 2D code labels identifying the product as “Authenticated” or safe. In order to simulate the detection of products with warnings, 1% of medicines are to contain a pre-programmed 2D code label to identify the product as either “dispensed elsewhere”, “recalled pack” (1%), “recalled product” (1%) or “product expired”, products with intentional warning labels are to be placed on randomly allocated boxes, in randomly allocated areas within each product location. Warning labels must be placed on both loose products and groups of products enclosed in clear plastic sheath to maintain error message label randomisation. All products labelled with a pre-programmed 2D code containing a warning message must also have the corresponding batch number and expiry recorded on the 2D code database.

Study design:

A Study to Understand the Effects of Audio Alerts on the Authentication and Detection of Counterfeit Medicines

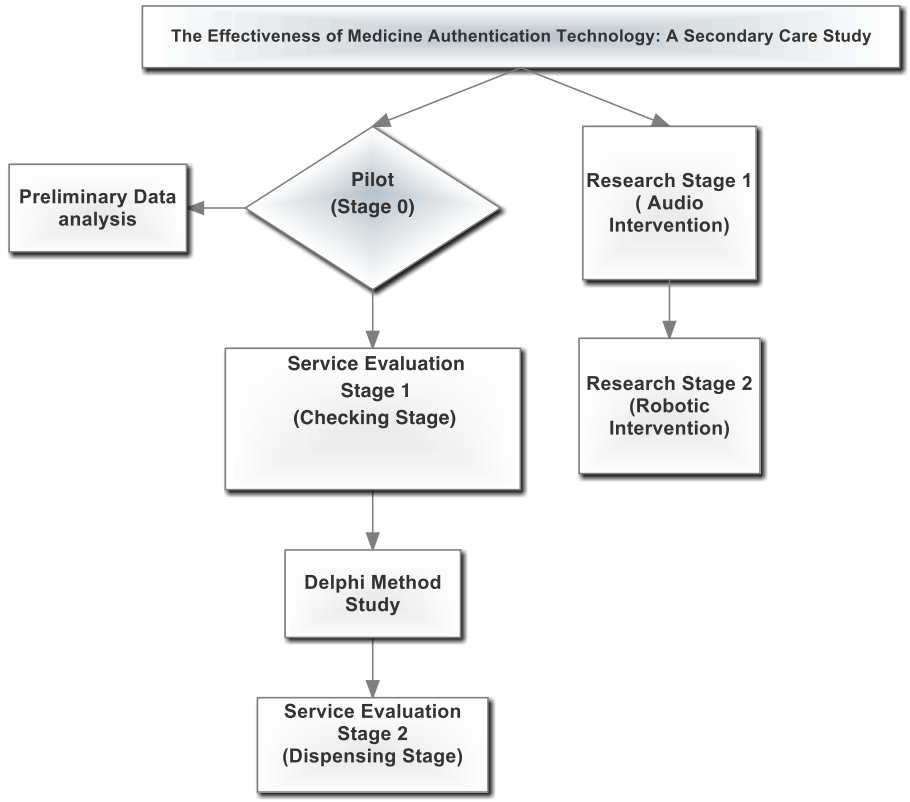


Figure 1:0: Schematic to illustrate the study design and to demonstrate that both the service evaluation and research stages occurred sequentially (i.e. not in parallel). Please note that research stages one and two will involve the comparison of results with those produced by the service evaluation study.

Study timeline:

Table 2.0: Medicine authentication study research stage one

	Oxford University Hospitals	Start	End	Dur
	Research Stage	4/7/16	12/1/17	189
1	Preparation	4/7/16	15/7/16	12
2	Stage 1	18/7/16	9/9/16	54
3	Stage 2	12/9/16	4/11/16	54
4	Basic Data Analysis	5/11/16	12/11/16	8
5	Complete Data Analysis	1/12/16	12/1/17	40

Stage one:

Week -2: An educational presentation will be followed by the consent procedure. Consent forms must be signed before week one of the study. This process will be supported by the chief pharmacist.

Week 1-6: The study must begin officially at the checking stage by qualified checking staff. Labels must be attached as per restrictions above including 4% of warning labels (1% x each of the 4 warning categories). A copy of the protocol must be attached to an email to all Horton Hospital pharmacy staff to introduce stage 1 of the project.

Week 7-8: No further labels are to be attached and a two-week wash-out period must be permitted to minimise the number of test products remaining in the dispensary. On Friday of week 8 all remaining products on the shelf must be recorded on the database. (Research Stage 1 is to be conducted for a total of 8 weeks)

Expected results:

Research data will include data entered into the system, data retrieved by authentication technology and data detected by staff.

The following results will be achieved for stage 1.

Quantitative results will include:

1. Operational Authentication Rate (%) (OAR)
2. Technical Detection Rate (%) (TDR), Operational Detection Rates (ODR1 and ODR2) (%)
3. Identification of commonly un-authenticated medicines
4. Identification of commonly un-detected medicines
5. MAS down time
6. MAS response time
7. Incidence of false positives

The results of this study are expected to be published in the first quarter of 2017. *This protocol was produced in line with the spirit checklist [9].*

Participant requirements

Manual authentication procedure- falsified, expired and recalled medicines

1. Start up the desktop computer (p.c) on the checking bench.
2. Log on to the p.c using user name and password.
3. On the desktop, select the patient medication record software (PMR) icon and sign in using username and password.
4. Select the Aegate function.
5. This will bring up a grey screen, with two input fields labelled EAN barcode and 2D barcode.

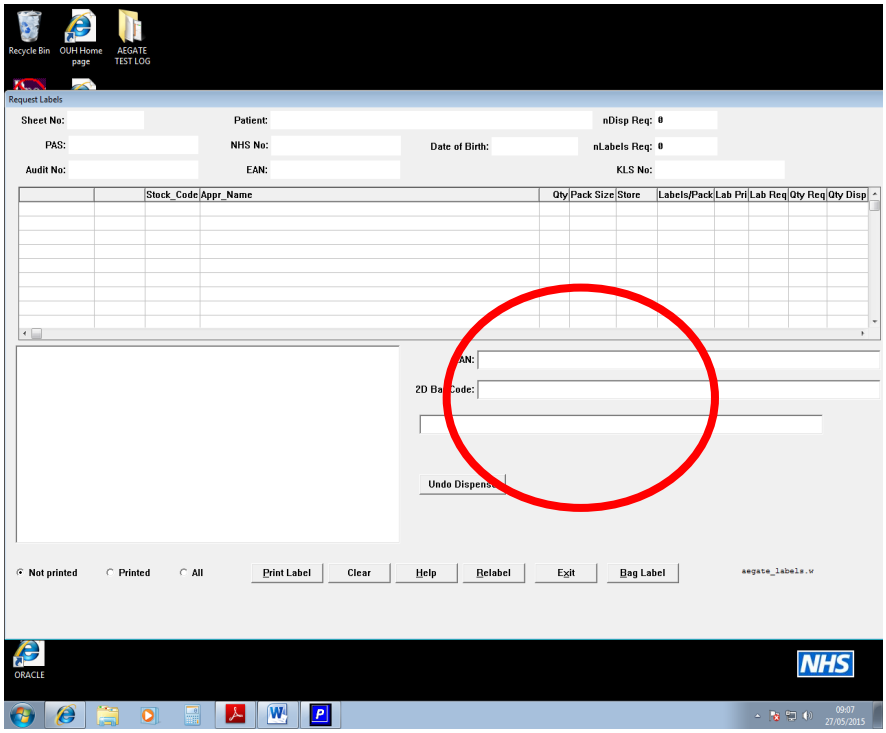


Figure 1.0: Screenshot displaying data input fields

6. Only products with a small purple label beside the expiry date are included in this study.

Figure 2.0: Image showing the purple sticker attached to study medicines

7. It is advised that scanning of all products is completed before starting the professional checking process.

8. If the product you are checking contains a small purple label (point 6) simply scan the EAN barcode on the box (see below), this should generate a line of text that describes the product.

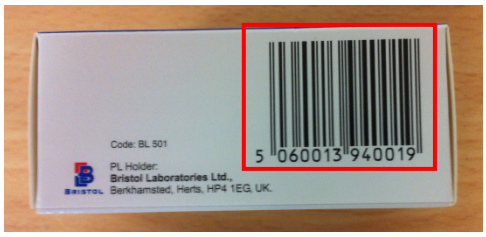


Figure 3.0: The barcode which must be scanned initially

9. Scan the 2D barcode box which will be located next to or at the opposite end to the expiry date and batch number (see below) (Please note that the cursor should automatically begin in the EAN barcode field and after EAN scanning, it should migrate to the 2D barcode field).

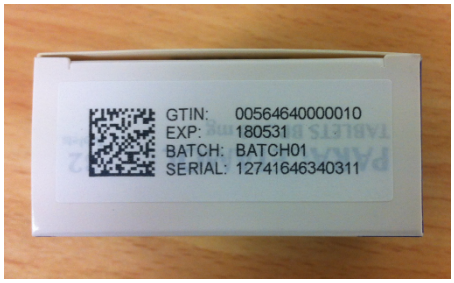


Figure 4.0: The 2D data matrix to be scanned directly after linear barcode scanning

10. Once the 2D barcode is scanned a small purple Aegate symbol beside the 2D barcode field will appear to highlight the medicine as authenticated. This symbol can be double clicked to expand which allows the user to read the messages associated with each product.

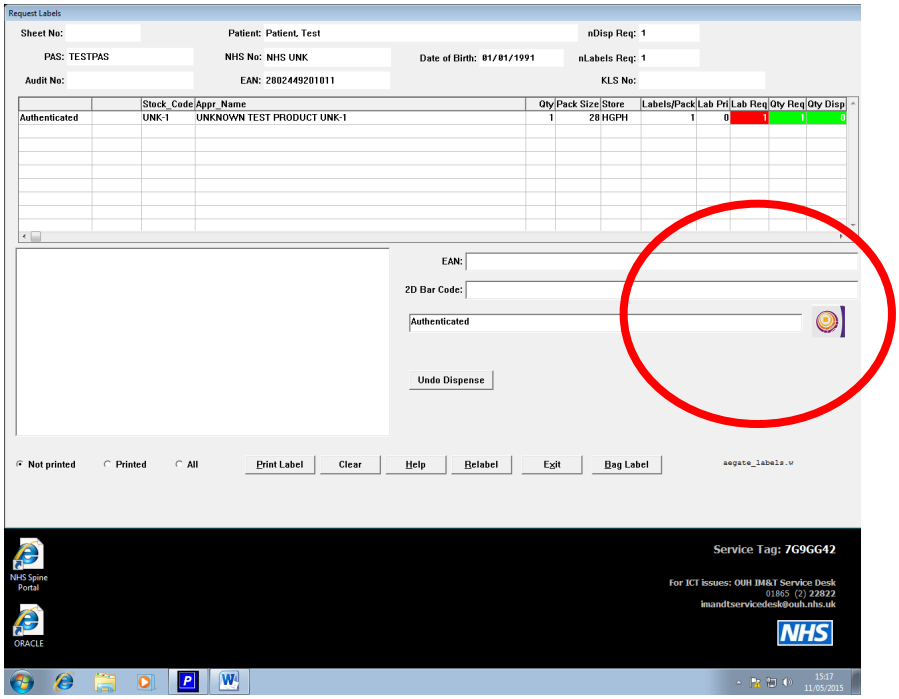


Figure 5.0: A screenshot displaying the purple 'Authenticated' symbol.

If the product is suspicious, expired, batch recalled, product recalled, dispensed elsewhere, then a large Red message will pop up to indicate the status of the medicine. If the product is a split pack it is likely that it will have already been authenticated at this dispensary and will therefore display Amber message stating “Already dispensed here” (This product is safe to be dispensed). See example below.

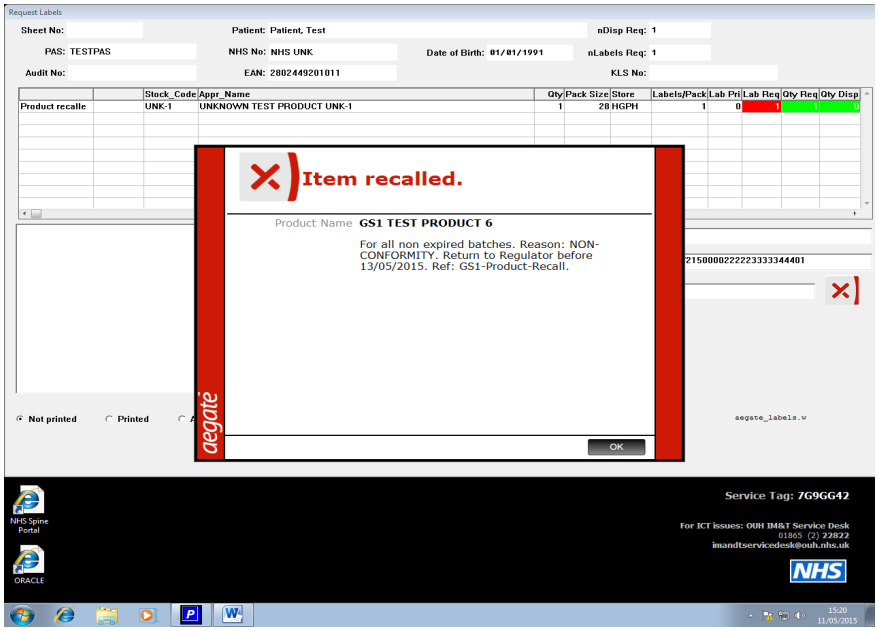


Figure 6.0: A screenshot displaying the type of message which appears.

11. All products authenticated that day will remain on screen until the application is closed. This gives the operator an option to recheck product status by double clicking on the product scanned on screen.

12. A message may appear to say “Item scan is invalid please scan product again") if this occurs please close PMR software and re-open as per protocol. When re-opened please re-scan the product to ensure the product has been scanned. If the system declares that the product has been “already dispensed here” this signifies that

the initial message was transmitted. In this instance please highlight the product in question and click undo.

13. If a red warning message appears after 2D scanning then remove the product and place in the quarantine area.
14. If the product scanned with warning is the last of its kind in the dispensary and is for urgent use then simply write down the 2D barcode information on the log of medicines with warning (Or remove 2D barcode sticker if possible and place on the list) also detailing the product name, strength, formulation and if otherwise suitable dispense as normal. (The 2D barcodes on these products contain pre-programmed messages and do not relate to the real status of the medicine). If the medicine is otherwise fit for delivery to the patient according to departmental procedure checks then this medicine can be checked and delivered to the patient.

16. If a product is authenticated in error or requires returning to stock please highlight the product in question and press the undo button. The product will remain on screen but will be classed as not verified.

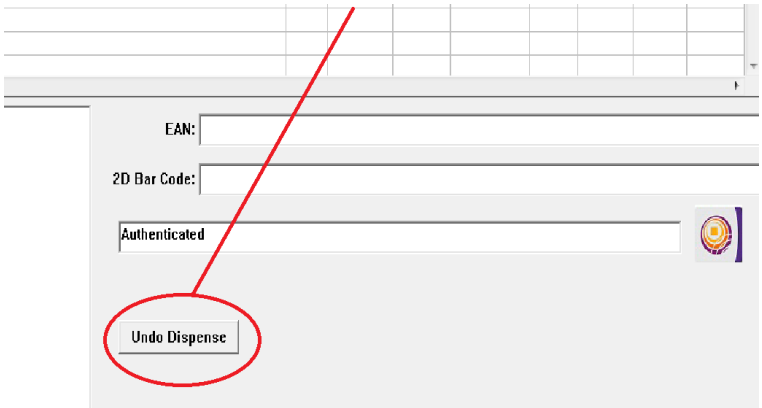


Figure 7.0: A screenshot identifying the 'Undo' button, requiring to reverse medicines authenticated in error.

Please note: Scanning is only necessary for products that contain a purple sticker beside their expiry date and a 2D label on their product box.

Please note: Some medicine containers may have two 2D labels, one printed onto the box by the manufacturer and one fixed to the box by the researcher. Please only scan the larger adhesive label. Please see service log below and record service errors, feedback/complaints, log of medicines with warnings or medicines dispensed as stock without being authenticated.

Service Logs

Log of service errors or incidents

Date	Error / Incident

Log of complaints or feedback

Date	Complaint / Feedback

Log of medicines with warnings / Products issued as stock and labels removed

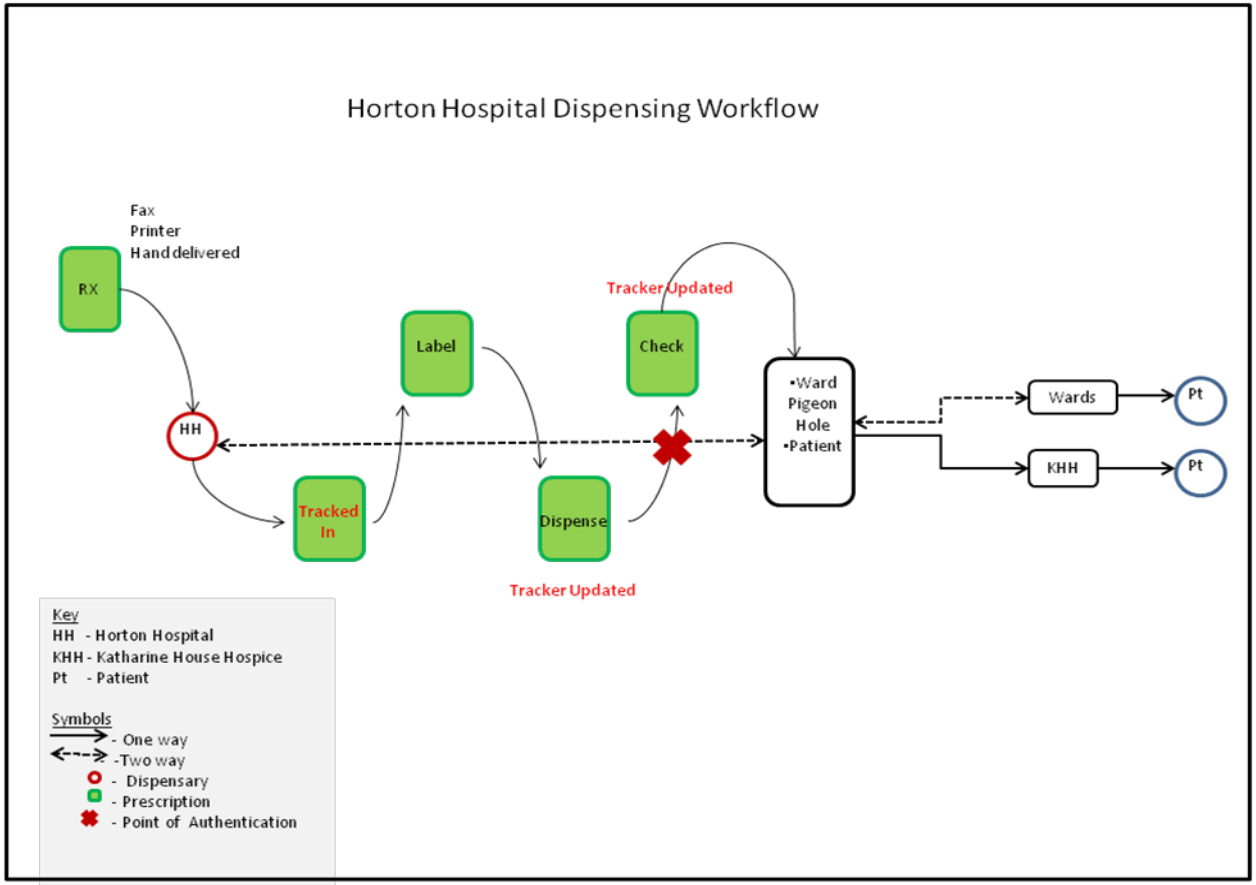
Medicine name and Warning/removed as stock	2D Barcode / 2D barcode details

Table 1.0: Total portfolio of medicines included in study.

Value	**Volume Dispensed**
Afatanib 40mg injection	Paracetamol 500mg tablets
Aflibercept injection 40mg/ml	Codeine 30mg tablets
Bosutinib 500mg injection	Omeprazole 20mg capsules
Botulinum toxin type A injection 100 units	Prednisolone 5mg tablets
Darbopoetin alpha 300 mcg injection	Co-amoxiclav 625mg tablets
Dexamethasone 2mg tabs	Macrogol 3350 sachets 13.125g
Ferric Carboxymaltose injection 50mg/ml	Lactulose 300 ml liquid 10g/15ml
Infliximab 100mg infusion	Dalteparin 5000 units syringe
Lenalidomide 10mg tablets	Aspirin 75mg tablets
Lenalidomide 25mg tablets	Ibuprofen 400mg tablets
Linezolid 600mg tablets	Piperacillin/Tazobactam 4.5g injection

Pomalidamide 1mg tablets	Adcal d3 tablets 1500mg/ 400 units
Rivaroxaban 15mg tablets	Salbutamol inhaler 100mcg
Trastuzumab 600mg injection	Morphine Sulphate 10mg/5ml solution
Pentosan polysulphate 100mg capsules	Tramadol 50mg capsules

This table lists the top 15 products by value and top 15 products by transaction, extracted from the initial portfolio of 87 lines. This range of medicines contains the most highly counterfeiting medicine categories by clinical indication, which includes oncology/cytostatics, musculoskeletal, respiratory, central nervous system, cardiovascular and anti-infective [10


Horton Hospital Dispensing Workflow
Fax
Printer
Hand delivered
RX
HH
Tracked In
Label
Dispense
Tracker Updated
Check
Tracker Updated
•Ward
Pigeon
Hole
•Patient
Wards
KHH
Pt
Pt
Key
HH - Horton Hospital
KHH - Katharine House Hospice
Pt - Patient
Symbols
- One way
-Two way
- Dispensary
- Prescription
- Point of Authentication

The Optimisation of a Medicines Authentication Technology

The impact of a robotic dispensing system on the detection of counterfeit medicines (Proposed but not conducted)

Protocol 002: Research Stage 2

Author: Bernard Naughton

Protocol Version	Date
3.0	06/0/15

Funding: Aegate Ltd, Keele University and the University of Oxford.

Study Site: The Churchill Hospital or John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust.

Roles and Responsibilities:

Primary Investigator: Mr. Bernard Naughton (University of Keele, University of Oxford and Oxford University Hospitals).

Senior Tutors: Professor Stephen Chapman (Keele University) and Dr. David Brindley (University of Oxford)

Commercial Sponsor Representative: Mr. Paul Thomas (Aegate Ltd).

AHSN Representative: Dr. Lindsey Roberts.

OUHFT Representatives: Mrs. Emma Pullan and Mr. Bhulesh Vadher.

Pilot Sponsor: Keele University

The funding source provider had no role in the design of this study, execution of this study, data analysis or decision to publish.

A steering group committee meeting took place on November 11th 2015 at the University of Oxford Said Business School. The following is a list of all attendees. Prof. Sue Dopson (Oxford), Prof. Stephen Chapman (Keele), Dr. David Brindley (Oxford), Dr. Nick Scott-Ram (AHSN), Dr Lindsey Roberts (AHSN), Mr. Bernard Naughton (Keele/Oxford/ OUHFT), Mark Di Simone (Aegate), Paul Thomas (Aegate), Emma Pullan (OUHFT), Bhulesh Vadher (OUHFT/AHSN) Cristiano Ressi di Cerviav (Aegate).

Apologies: Professor Sir John Bell (Oxford), Graham Smith (Aegate) and Professor Georg Hollander.

Ethics approval: TBC

Background and Rationale:

See protocol 001.

Methods:

Study Setting – A large teaching hospital with robotic dispensing system.

Product Identification:

See protocol 001

Labelling Procedure

See protocol 001.

Pilot design:

Research Stage: A study to compare baseline pilot data with an optimised variation.

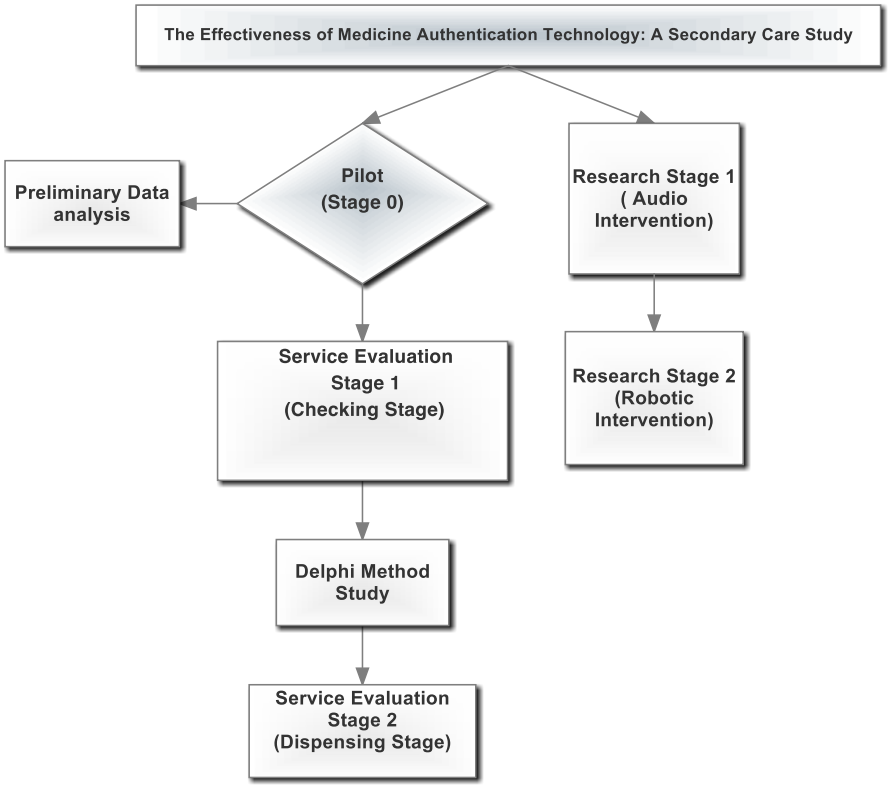


Figure 1:0: Schematic to illustrate the study design and to demonstrate that both service evaluation and research stages are researched sequentially (i.e. not in parallel).

Study Timeline:

Table 2.0: Research stage: hospital pilot timeline

	Oxford University Hospitals	Start	End	Dur
	Research Stage	4/7/16	12/1/17	189
1	Preparation	4/7/16	15/7/16	12
2	Stage 1	18/7/16	9/9/16	54
3	Stage 2	12/9/16	4/11/16	54
4	Basic Data Analysis	5/11/16	12/11/16	8
5	Complete Data Analysis	1/12/16	12/1/17	40

Research:

Stage two:

Week -2: An educational presentation will be followed by the consent procedure. Consent forms must be signed before week one of the study. This process will be supported by the chief pharmacist.

Week 1-6: The study must begin officially at the checking stage by qualified checking staff (the same group type involved in stage one). Labels must be attached as per restrictions above including 4% of warning labels (1% x each of the 4 warning categories). A copy of the protocol must be attached to an email to all Horton Hospital pharmacy staff to introduce research stage 2 of the project during week 3.

Week 7-8: No further labels are to be attached and a two-week wash-out period must be permitted to minimise the number of test products remaining in the dispensary. On Friday of week 8 all remaining products on the shelf must be recorded on the database. (Authentication at the checking stage is to be conducted for a total of 8 weeks)

The robot dispensing system will automatically authenticate each medicine as it is dispensed from the robotic unit. If a medicine containing a pre-programmed error code is scanned it will alert staff. The robot will remove the product from the unit and place it in a separate area with a label affixed highlighting the product as potentially dangerous. The accredited checking staff will then remove the product and place it in a quarantine area. See robotic authentication procedure below.

Expected results:

Output will include data entered into the system, data retrieved by authentication technology and data detected by staff.

The following results will be achieved for stage 1 and stage 2.

Quantitative results will include:

1. Robotic Authentication Rate (%) (RAR)
2. Robotic Detection Rate (%) RDR
3. Technical Detection Rate (%) (TDR),
4. Operational Detection Rate (ODR) (%)
5. Identification of commonly un-authenticated medicines
6. Identification of commonly un-detected medicines
7. MAT down time
8. MAT response time
9. The incidence of false positives

The results of this study are expected to be published in the third quarter of 2017. *This protocol was produced in line with the spirit checklist [9].*

Robotic authentication procedure: Falsified, expired and recalled medicines

1. The robot will be preconfigured to authenticate any medicine with a 2D barcode and this will occur without participant instruction or intervention.
2. Log on to the p.c on the checking bench using user name and password.
3. On the desktop, select the patient medication record software (PMR) and sign in using username and password.
4. Select the Aegate function.
5. This will bring up a grey screen, with two input fields labelled EAN barcode and 2D barcode.

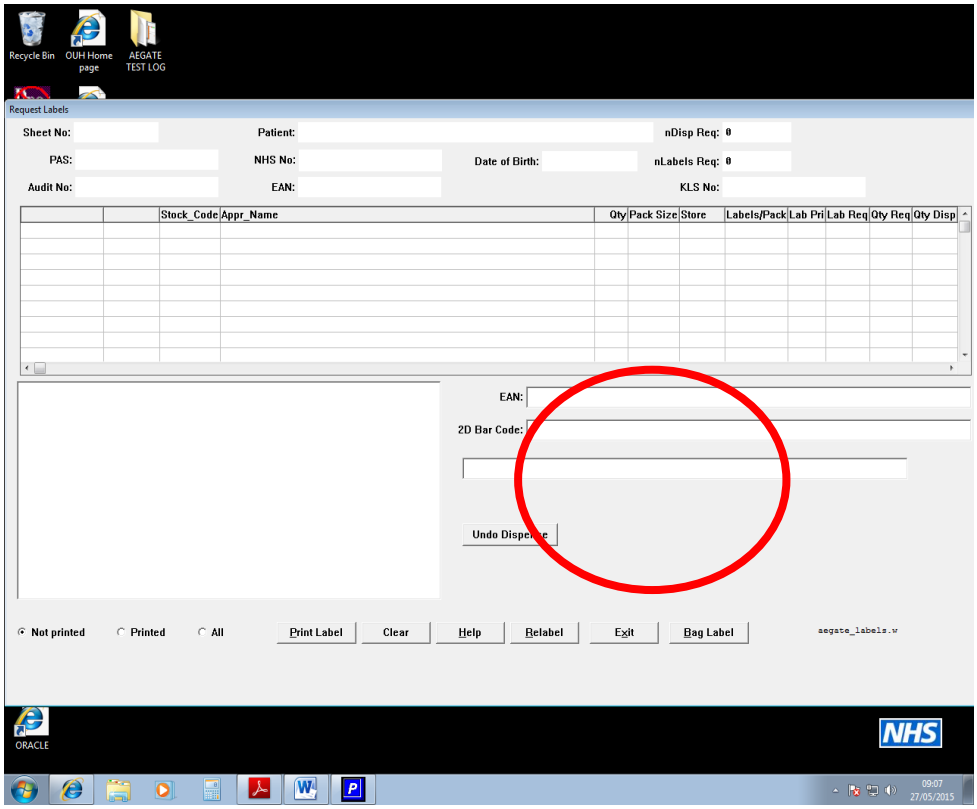


Figure 1.0: A screenshot identifying the EAN barcode and 2D data matrix data fields

6. Only products with a small purple label beside the expiry date are included in this study.

Figure 2.0: An image of a medicine with sticker which identifies it as being part of the study

7. All products will be scanned by the robot and appear on screen.

8. If the product you are checking contains a small purple label (point 6) this will automatically be scanned by the robot, this should generate a line of text that describes the product on screen.

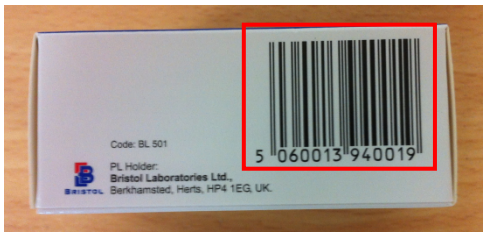


Figure 3.0: An image of medicine EAN barcode.

9. The robot will also scan the 2D barcode box which will be located next to or at the opposite end to the expiry date and batch number (see below) (Please note that the cursor should automatically begin in the EAN barcode field and after EAN scanning, it should migrate to the 2D barcode field).

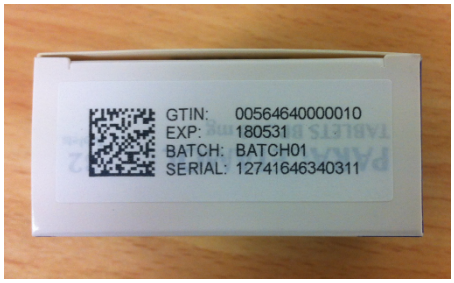


Figure 4.0: An image of a study medicine containing a 2D data matrix

10. Once the 2D barcode is scanned a small purple Aegate symbol beside the 2D barcode field will appear to highlight the medicine as authenticated. This symbol can be double clicked to expand which allows the user to read the messages associated with each product.

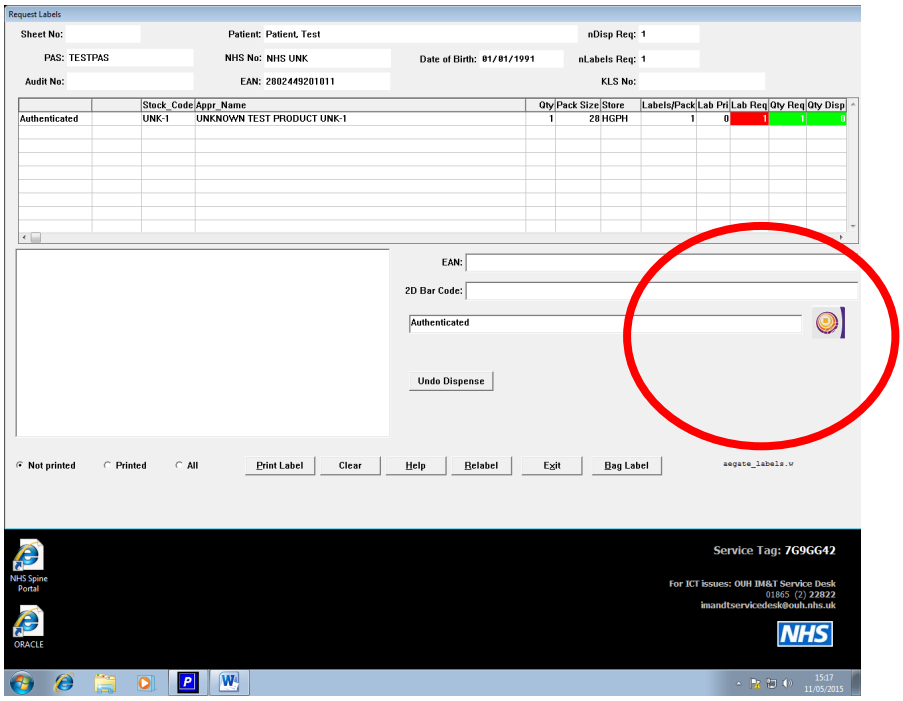


Figure 5.0: A screenshot of the Authentication technology integration with purple logo, which highlights that a product has been 'Authenticated'.

11. If the product is suspicious, expired, batch recalled, product recalled, dispensed elsewhere, then a large **Red** message will pop up to indicate the status of the medicine (a sound may also alarm depending on the results of research stage one, TBC). If the product is a split pack it is likely that it will have already been authenticated at this dispensary and will therefore display Amber message stating "Already dispensed here" (This product is safe to be dispensed). See example below. This is however unlikely as the robot should not be dispensing park packs.

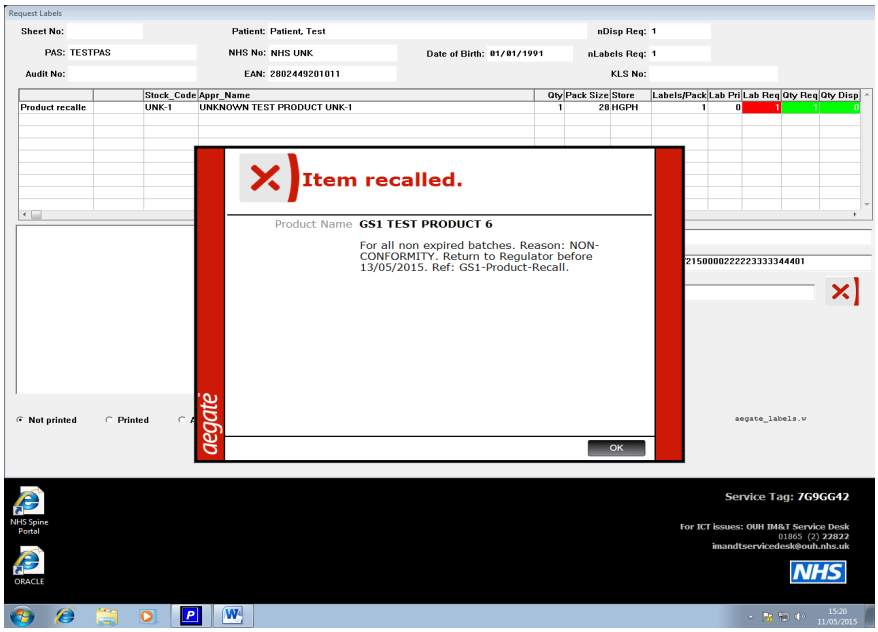


Figure 6.0: A screenshot displaying the message which appears when a recalled, expired or suspicious medicine is scanned.

12. All products authenticated that day will remain on screen until the application is closed. This gives the operator an option to recheck product status by double clicking on the product scanned on screen.

13. A message may appear to say “Item scan is invalid please scan product again “) if this occurs please close PMR software and re-open as per protocol. When re-opened please re-scan the product to ensure the product has been scanned. If the system declares that the product has been “already dispensed here” this signifies that the initial message was transmitted. In this instance please highlight the product in question and click undo.
14. If a **red** warning message appears after 2D scanning (with or without audio sounds) then the product will be labeled with a warning label to identify it as potentially dangerous. Remove the product and place in the quarantine area.
15. If the product scanned with warning is the last of its kind in the dispensary and is for urgent use then simply write down the 2D barcode information on the log of medicines with warning (Or remove 2D barcode sticker if possible and place on the list) also detailing the product name, strength, formulation and if otherwise suitable dispense as normal. (The 2D barcodes on these products contain pre-programmed messages and do not relate to the real status of the medicine). If the medicine is otherwise fit for delivery to the patient according to departmental procedure checks then this medicine can be checked and delivered to the patient.

16. If a product is authenticated in error or requires returning to stock please highlight the product in question and press the undo button. The product will remain on screen but will be classed as not verified.

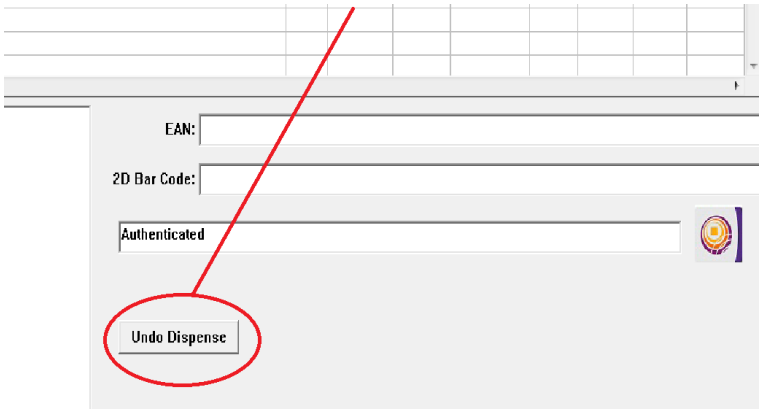


Figure 7.0: A screenshot highlighting the 'Undo' button, required when a medicine has been authenticated in error.

Please note: Scanning is only necessary for products that contain a purple sticker beside their expiry date and a 2D label on their product box.

Please note: Some medicine containers may have two 2D labels, one printed onto the box by the manufacturer and one fixed to the box by the researcher. Please only scan the larger adhesive label. Please see service log below and record service errors, feedback/complaints, log of medicines with warnings or medicines dispensed as stock.

Service Logs

Log of service errors or incidents

Date	**Error / Incident**

Log of complaints or feedback

Date	Complaint / Feedback

Log of Medicines with warnings / Products issued as stock and labels removed

Medicine name and Warning/removed as stock	2D Barcode / 2D barcode details

Product Selection

See procedure for selection in protocol 002. Product selection is dependent on which site is used for research stage

Appendix 3:0 Data cleansing and analysis form

UK- pilot- serial codes

1. Starting with ‘authenticated + authenticated elsewhere', custom sort column M (full pack 2/10/15) in alphabetical order and remove data described as a full pack as of 2/10/15. Repeat this for all groups.

2. Remove data recorded as ‘removed as stock’ (n=__ from disp. identified warnings)

3. Select a group (i.e. authenticated + authenticated elsewhere, expired, pack recalled or product recalled) Select all data in the selected group < Sort by stage< highlight by stage to calculate the number of 2D data labels entered by category in each group.

   (This process allowed the researcher to identify the number of medicines included in the study, taking into consideration those that were remained on the shelves at the end of the study)

Complete table below

			UK Pilot Serial codes – Data in				
		Authenticated	Auth. Elsewhere	Pack Recalled	Pack Expired	Product Recalled	Already Dispensed here
Horton	Stage 0						
Horton	Stage 1						
Horton	Stage 2						
CH1 + CH 2	Testing						
JR1 + JR2 (1M57V02 + 2W09V02)	Testing						

Authentication Data

1. Total scans identified by the software. n=___

2. Study periods (Stage 0: 1/6/15 – 12/6/15, Stage 1: 15/6/15- 7/8/15, Stage 2: 10/08/15 – 2/10/15) Remove scans, prior to 1/6/15 and post 2/10/15 (validation periods) – (n= __+__)

3. Create, and label new column (K) as "stage". Split data into stages according to the data scanned. Removing scans that occurred during weekends between study periods 0-1 and 1-2. (n= _+ _)

4. Custom sort date by dispensary (column C) in alphabetical order, remove all non-dispensary scans from column C I.e. Researchers PC (Processed to generate dispensed elsewhere message) (n= ___).

5. Highlight the JR and CH dispensary scans in blue and green respectively for ease of identification.

6. Sort each dispensary by EVENT and remove NONDISPENSE from each dispensary separately CH (n=_), JR (n=_), Horton (n=_)

7. (Non-dispense is when a staff member pressed undo after authenticating or the system is down and recorded the attempt as unsuccessful)

8. Select JR dispensary group and custom sort by response code in alphabetical order. All response codes are now grouped. Highlight each response code groups serial codes and click remove duplicates. E.g. JR authentication, highlight all serial codes with

an authentication response code, and select remove duplicates on the ‘Data’ tab on

9. Microsoft excel, unselect all and select Column F. Continue this process for each response code in each dispensary with the exception of ‘Already dispensed here’. JR (N= __ x already dispensed here, N= __ x authenticated, N= __ x pack expired, N= __ x pack recalled, N= __ x product recalled). CH (N= __ x already dispensed here, N= __ x authenticated, N= __ x pack expired, N= __ x pack recalled, N= __ x product recalled). Horton (N= __x already dispensed elsewhere, N= __ x authenticated, N= __ x pack expired, N= __ x pack recalled, N= __x product recalled)

10. Total scans remaining. N= ___

Complete the results table below to summarise scanning numbers by category

		Database	**Authentication Data – Data Generated**				
		Authenticated	Auth. Elsewhere	Pack Recalled	Pack Expired	Product Recalled	Already Dispensed here
Horton	Stage 0						
Horton	Stage 1						
Horton	Stage 2						
CH1 + CH 2	Testing						
JR1 + JR2 (1M57V02 + 2W09V02)	Testing						

Appendix 4.0: Ethical approval letters (NHS R&D, HRA and University) and consent form.

Keele University

Ref: ERP2289

6th July 2016

Bernard Naughton
ISTM
Keele University

Dear Bernard

Re: The Investigation and Optimisation of a Medicines Authentication System to Detect Counterfeit Medicines

Thank you for submitting your revised application for review. I am pleased to inform you that your application (**Phase 1 and 2**) has been approved by the Ethics Review Panel. The following documents have been reviewed and approved by the panel as follows:

Document(s)	Version Number	Date
Staff Consent Form (Chief Pharmacist Research Stages 1 and 2)	3	07-06-2016
Protocol 001 and 002	3	06-06-2016

As previously discussed, the Panel understand that you will be submitting a separate application for NHS REC and HRA approval for the third phase of this project, which involves NHS patients.

If the fieldwork goes beyond the date stated in your application, **8th October 2017**, or there are any other amendments to your study you must submit an 'application to amend study' form to the ERP administrator at research.erps@keele.ac.uk stating **ERP2** in the subject line of the e-mail. This form is available via http://www.keele.ac.uk/researchsupport/researchethics/

Directorate of Engagement & Partnerships
T: +44(0)1782 734467

Keele University, Staffordshire ST5 5BG, UK
www.keele.ac.uk +44 (0)1782 732000

Ref: ERP2289

7th December 2016

Bernard Naughton
ISTM
Keele University

Dear Bernard

Re: The Investigation and Optimisation of a Medicines Authentication System to Detect Counterfeit Medicines

Thank you for submitting your second application to amend study, informing us of the addition of semi-structured interviews with a purposive sample. I am pleased to inform you that your application has been approved by the Ethical Review Panel. The following documents have been reviewed and approved by the Panel as follows:-

Document	Version	Date
Survey Monkey	1	05-12-2016
Research Protocols 001 and 002	4	05-12-2016

If the fieldwork goes beyond the date stated in your application, **8th October 2017**, or there are any other amendments to your study you must submit an 'application to amend study' form to the ERP administrator at research.erps@keele.ac.uk stating **ERP2** in the subject line of the e-mail. This form is available via http://www.keele.ac.uk/researchsupport/researchethics/

If you have any queries, please do not hesitate to contact me via the ERP administrator on research.erps@keele.ac.uk stating **ERP2** in the subject line of the e-mail.

Regards

Yours sincerely

pp C H Bonnerman

Dr Colin Rigby
Chair – Ethical Review Panel

CC RI Manager
Supervisor

Directorate of Engagement & Partnerships
T: +44(0)1782 734467

Keele University, Staffordshire ST5 5BG, UK
www.keele.ac.uk +44 (0)1782 732000

02/02/2018

Dear Bernard

PI: Bernard Naughton
Title: The Safe Purchase of Medicine: An Anonymous General Public Health Survey
Ref: ERP2369

Thank you for submitting your application for review. The proposal was reviewed by full Panel. I am pleased to inform you that your application has been approved by the Ethics Review Panel.

If the fieldwork goes beyond the date stated in your application, or there are any amendments to your study you must submit an 'application to amend study' form to the ERP administrator at research.governance@keele.ac.uk. This form is available via http://www.keele.ac.uk/researchsupport/researchethics/

If you have any queries please do not hesitate to contact me, in writing, via the ERP administrator, at research.governance@keele.ac.uk stating **ERP2369** in the subject line of the e-mail.

Yours sincerely
PP.

Dr Colin Rigby
Chair – Ethical Review Panel

NHS
Health Research Authority

Mr Bernard Naughton
Said Business School
Park End Street
Oxford
OX1 1HP

Email: hra.approval@nhs.net

05 September 2016

Dear Mr Naughton

Letter of HRA Approval

Study title:	**The Investigation and Optimisation of Medicine Authentication Technology: A Secondary Care Study**
IRAS project ID:	**210334**
Protocol number:	**n/a**
Sponsor	**Keele University**

I am pleased to confirm that **HRA Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details

HH/FM/PID:12284

Oxford University Hospitals NHS

NHS Foundation Trust
From the Head of Research Governance
OUH Research & Development
Joint Research Office
Block 60, Churchill Hospital
Old Road, Headington
Oxford OX3 7LE

Tel: (01865) 572973
Fax: (01865) 572242
Foteini.Mavrommati@ouh.nhs.uk

Mr Bernard Naughton
Said Business School
Park End Street
Oxford
OX11HP

30 September 2016

Dear Mr Naughton,

Re: The Investigation and Optimisation of Medicine Authentication Technology: A Secondary Care Study
IRAS Reference: 210334
Research and Development Reference: 12284
Research Ethics Committee Reference: ERP2289

Confirmation of Trust Management Approval

On behalf of the Oxford University Hospitals NHS Foundation Trust, I am pleased to confirm Trust Management Approval and Indemnity for the above research on the basis described in the application, protocol and other supporting documents.

Conditions of Approval

Your attention is drawn to the attached conditions of approval. Breach of these conditions may result in Trust Management Approval being revoked.

Recruitment

The agreed total recruitment target for your study at the OUH site is 25- 50 participants by 08 October 2017 as specified in the Contract.

Your first participant recruitment target date is 06 December 2016.

To support OUH Trust and national recruitment targets, R&D will monitor and publish recruitment for your study: 1. Performance against the 70 calendar day period benchmark from the time of receipt of a valid research application in R&D to the date of recruitment of first participant to your study; and for interventional trials; 2. Recruiting planned participants to time and target. The R&D office will contact you to request recruitment progress against both targets. If you recruit your first participant into the study then please send the date to researchrecruitment@ouh.nhs.uk. If you miss this target you will be required to give reasons that can be reported to the DOH/NIHR.

In order to facilitate good communications and avoid unnecessary delays please copy all correspondence with the Research Ethics Committee (REC) to R&D, providing copies of all relevant documents.

Oxford University Hospitals NHS
NHS Foundation Trust

Oxford Academic Study

Ref: BN_001

7th June 2016

A partnership project with Keele University, Oxford University, Aegate Limited, Oxford University Hospitals NHS Foundation Trust and the Oxfordshire Academic Health Science Network.

Oxford University Hospitals NHS Trust Consent Form

I [enter name here] ..... am an employee of Oxford University Hospitals NHS Foundation trust, Pharmacy department and consent to the research described in the attached authentication protocol.

I have read the research protocol and understand all that is expected of me and am willing to be fully compliant with research stages one or two

Signed:

.....
Oxford University Hospitals, Pharmacy Department.

If you have a concern about any aspect of this project, please contact Bernard Naughton (bernard.naughton@keele.ac.uk or bernard.naughton@sbs.ox.ac.uk mailto:) or Professor Stephen Chapman (s.r.chapman@keeele.ac.uk) and they will do their best to answer your query. The researcher should acknowledge your concern within 10 working days and give you an indication of how he intends to deal with it. If you remain unhappy or wish to make a formal complaint, please contact the Chair of the Ethical Research Panel 2 at the University of Keele (using the contact details below) who will seek to resolve the matter in a reasonably expeditious manner:

Chair, Ethical Research Panel 2, Keele University. Email : research.erps@keele.ac.uk :Innovation Centre 2, Keele University Science & Innovation Park, Keele University, Staffordshire, ST5 5NH, UK, Telephone: 01782 734495.

Ref: ERP2289

7th October 2016

Bernard Naughton
ISTM
Keele University

Dear Bernard

Re: The Investigation and Optimisation of a Medicines Authentication System to Detect Counterfeit Medicines

Thank you for submitting your application to amend study, informing us of a typographical error within the Consent form. I am pleased to inform you that your application has been approved by the Ethical Review Panel. The following document has been reviewed and approved by the Panel as follows:-

Document	Version	Date
Staff Consent Form (Chief Pharmacist Research Stages 1&2)	4	05-10-2016

If the fieldwork goes beyond the date stated in your application, **8th October 2017**, or there are any other amendments to your study you must submit an 'application to amend study' form to the ERP administrator at research.erps@keele.ac.uk stating **ERP2** in the subject line of the e-mail. This form is available via http://www.keele.ac.uk/researchsupport/researchethics/

If you have any queries, please do not hesitate to contact me via the ERP administrator on research.erps@keele.ac.uk stating **ERP2** in the subject line of the e-mail.

Regards

Yours sincerely

pp C H Bonnerman

Dr Colin Rigby
Chair – Ethical Review Panel

CC RI Manager
Supervisor

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Appendix 5.0: Complete Delphi study results

Round one

Table 1.0: This table lists each question used in the survey, whether consensus was met and the average result from round one.

No.	Question	Consensus (Yes/No)	Result (median score) Rating = 1-7 (r) Likert Like= 1-5/1-4 (p) Descriptive: 5 options (d)
1	Demographic	x	x
2.	Demographic	x	x
3.	Demographic	x	x
4.	Based on your experience of the Medicines Authentication System (MAS), how would you rate its general speed on a scale of 1 to 7? (1 represents very slow and 7 represents very fast)	Yes	6.00/7 (r)
5.	Based on your experience of the MAS, how would you describe its usability on a scale of 1 to 7? (1 represents very difficult and 7 represents very easy)	Yes	6.50/7 (r)
6.	There were some system errors reported by the MAS users throughout the pilot. On a scale of 1 to 7, how often did you experience these types of errors? (1 represents never and 7 represents very often) (These errors may have included issues with reading the 2D barcode, duplication of the scan on screen or warnings such as "The system has no resources",” item can is	Yes	1.00/7 (r)

	invalid please scan product again" or "test product not found")		
7.	The following are a list of reported, proposed improvements. Please rank them in order of importance (1-5)		
(i)	Remove/Solve the " Item can is invalid please scan product again " warning	Yes	4.00 (Less important) (l)
(ii)	Change the medicine scanning list on screen to ensure the last scanned item appears on the top of the list	Yes	1.00 (Important) (l)
(iii)	Include less product lines in the pilot study	Yes	4.50 (Less important) (l)
(iv)	Review the pop-up screens as the Red "Warning" screens could be mistaken for the common "Already dispensed here" screen.	Yes	2.00 (Important) (l)
(v)	Incorporate "important information" pop-ups into the authentication system	Yes	2.50 (mean) (Important) (l)
8	Excluding the suggestions above, please describe any other changes that you think could be made to improve the MAS or the Pilot.	No (Suggestions categorized as themes and included in round 2)	
9	How would you rate your understanding of the terms "Medicine Verification" and " Medicine Authentication"?		
9(I)	Medicines Verification	Yes	Average (d)
(ii)	Medicines Authentication	Yes	Average (d)
10	How would you rate the impact of the MAS on the service you provide on a scale of 1 to 7? (1 represents very disruptive and 7 represents not disruptive at all)	No (Reworded and included in round 2)	

11	It has been established during this pilot that not all medicines were scanned (authenticated) before being handed out to our patients. In the future, this may result in patients receiving expired, recalled, unsuitable or falsified/counterfeit medicines. Please, can you list three suggestions that may increase the rate of authentication of medicines (in order of importance)?	No (Suggestions categorized as themes and included in round 2) Median = 5.5 (δ 1.2)	
12	There have been occasions where products have been handed out despite showing a red pop-up box warning. Please list three suggestions of how this occurrence might be reduced (in order of importance).	No (Suggestions categorized as themes and included in round 2)	
13	How would you describe this survey's ease of completion?	Yes	About right/Easy (d)
14	How would you describe the length of this survey?	Yes	About right (d)
15	Please suggest any amendments that may improve this survey	No 3 suggestions made. All considered for round 2.	

Round Two

Table 2:0: This table lists each question used in the survey, whether consensus was met and the average result from round one.

No	Question	Consensus (Yes/No)	**Result** (median score) Rating = 1-7 (r) Likert Like= 1-5/1-4 (p) Descriptive: 5 options (d)
1	Demographic		
2.	Demographic	x	x

3.	Demographic	x	x
4	During round one we asked how you would rate the impact of the MAS on the service that you provide on a scale of 1 to 7? (1 represents very disruptive and 7 represents not disruptive at all). There appeared to be a difference of experience in terms of impact, the question and choices have been amended (below) to make the options clearer. Question 4: How would you rate the impact of the MAS on the service you provide on a scale of 1-7 (where 1 represents very disruptive and 7 represents very helpful).	Yes	4.00(r) (Not disruptive)
5.	During round one of this survey, further suggestions were made to improve the Medicines Authentication System (MAS) or the pilot. Please rank the suggested changes below in the order of importance (1 being most important and 5 being least important).		
(i)	Split Pack Count Down (A function to identify how many tablets were used for each dispensing if not a full pack) (MAS)	Yes	5.00 (Less Important) (l)
(ii)	Sounds could also be enabled to ensure warnings/information are noticed (MAS)	Yes	2.50 (Important) (l)
(iii)	Clearer Terminology of Warnings (MAS)	No	4.00 (No result) (l)
(iv)	Cover the manufacturers 2d barcode to avoid these being scanned in error (Pilot)	No	3.00 (No result) (l)

(v)	Make the symbol indicating an item that needs to be scanned larger/more visible (Pilot)	Yes	1.0 (Important) (l)
6	During round one of this survey, there were a variety of suggestions made to increase the Rate of Authentication (scanning). Valid suggestions were subdivided into three categories 1. Process Change 2. Technology change and 3. Education. In terms of Process Change please rank these suggestions in order of importance (with 1 being the most important and 5 being the least important)		
(i)	Make the symbol indicating an item that needs to be scanned larger/more visible (Process)	Yes	2.50 (Important) (l)
(ii)	A checkbox on scripts to tick once items authenticated (scanned) (Process)	No	2.5 (No result) (l)
(iii)	Sign the barcode when scanned out (Process)	Yes	3.0 (No result) (l)
(iv)	More terminals available for scanning products could place them at various locations in the dispensary and then have a big screen so you can see that products have been authenticated (Process)	Yes	5.00 (Less important) (l)
(v)	Scan all products in the dispensary (Process)	No	3 (No result) (l)

7	During round one of this survey, there were a variety of suggestions made to increase the Rate of Authentication (scanning). Valid suggestions were subdivided into three categories 1. Process Change 2. Education and 3.Technology change In terms of Education and Technology change please rank these suggestions in order of importance (with 1 being the most important and 5 being the least important)		
(i)	Have a list of the drugs in the study by the dispensing benches as a double check (Education)	No	4.00 (no result)(l)
(ii)	An alarm that sounds when the items leave the department un-scanned (Technology Change)	No	5.00 (no result) (l)
(iii)	Education of staff on the importance of medicines authentication (e.g. examples of patient harm, figures that highlight the extent of the problem) (Education)	No	3.00 (no result)(l)
(iv)	A system change that knows how many items have been booked in and prescription is not able to be tracked out as verified until all medications have been authenticated (Technology Change)	Yes	2.50 (Important) (l)
(v)	Encourage dispensers to look at the expiry dates (Education)	No	2.50 (no result)

8	During round one we explained that there have been occasions where products have been handed out despite showing a Pop-up Warning Box. We asked you to list three suggestions of how this occurrence might be reduced. Valid suggestions were subdivided into two categories 1. Education and 2. Technology change. In terms of Education please rank these suggestions in order of importance (with 1 being the most important and 4 being the least important)		
(i)	Encourage the dispenser/checker to take action on the warnings (Education)	Yes	2.00 (important) (l)
(ii)	Have a list of the warnings near the scanning out computer so it is clearer for them (Education)	No	3.0 (no result) (l)
(iii)	Increase knowledge of those that manage the process (Education)	No	2.7 (no result) (l)
(iv)	System user training (Education)	No	2.5 (no result) (l)
9	During round one we explained that there have been occasions where products have been handed out despite showing a Pop-up Warning Box. We asked you to list three suggestions of how this occurrence might be reduced. Valid suggestions were subdivided into two categories 1. Education and 2. Technology change. In terms of Technology Change please rank these suggestions in order of importance (with 1 being the most important and 4 being the least important)		
(i)	Flashing Warning Box (Technology)	No	3.00(no result) (l)
(ii)	An audible alert to accompany the pop-up warning box (Technology)	Yes	1.00 (important) (l)

(iii)	Making it mandatory to complete an "Action Taken" documentation process so that staff scanning are prompted to think about what the red warning means and be accountable for it (Technology)	Yes	2.00 (Important)(l)
(iv)	An alarm triggered as the un-authenticated item leaves the department (Technology)	Yes	4.00 (less important) (l)
10	How would you describe this survey's ease of completion?	Yes	About right (d)
11	How would you describe the length of this survey?	Yes	About Right (d)
12	Please suggest any amendments that may improve this survey	8/14 answered n/a 2/14 made suggestions that were not related to the survey itself	

Appendix 6.0: Chapter six interview Guide

In 2015, a study was carried out at the Horton Hospital to assess the effectiveness of medicines authentication technology. It was decided that in an effort to improve this technology an audio alert would be included which would alert upon scanning of a medicine that required action (quarantine/other action). You have recently been involved in an eight-week study where an existing medicines authentication technology was adapted to include the suggested audio alert alongside a number of existing visual pop-up alerts. This semi-structured interview aims to gauge your opinion on that sound intervention. Results may be published anonymously. Do you consent to be involved in this part of the study?
Thoughts and Opinions of a Visual Pop-Up Accompanied by an Audio Alert
1. What is your job role?
Accredited Checking Technician
Pharmacist
2. How old are you?
3. How many years' experience in healthcare do you have? In the NHS or otherwise?
4. Have you used the medicines authentication technology with pop-up alerts (without audio alert) on more
than one occasion?
Yes
No
5. On how many occasions have you used the medicines authentication technology, with audio alert?
0
1
2-5
5-10
Greater than ten times
6. During the recent 8-week study did you scan a medicine which generated an audio alert alongside a
visual pop-up?
Yes

No
7. Did you think the inclusion of an audio alert had a negative or a positive impact on the detection of
expired, recalled or falsified medicines? And why?
Negative
Positive
I did not ever hear the audio alert when authenticating medicines
8. Please take a moment to think about your experience of the audio alert which alarmed at the detection
of an expired, recalled or potentially falsified medicine and explain your opinion on this sound. Feel free to
comment on the volume, the tone, the pitch, the duration or any other thoughts which relate to it.
9. A negative alert might be too regular, overly irritating or often ignored. A positive alert might be one
which draws attention to an important issue without being so irritating it distracts other from other work.
Would you describe this audio alert as being a negative or positive improvement and why?
Negative
Positive
10. Did you feel that the audio alert hindered or helped you to detect expired, recalled or potentially falsified
medicines? And why?
Hindered
Helped
11. Do you feel that the inclusion of an audio alert encouraged, discouraged or had no effect on
your authentication rate of medicines? And why?
12. Was the technology with the audio alert better or worse than the previous version (without audio)? And
why?
13. The following is a list of comments recorded by participants during this study, please would you like to
identify whether you agree or disagree with the comments and why? (comments will be supplied during the
interview)

14. Do you think that there was an occasion where you knew the medicine needed to be scanned and
didn't scan it? If so, why?
15. Do you think there was a time when you came across a medicine that required quarantine but didn't?
Why was that?
16. How does this audio alert compare to other Information Technology (IT) alerts you are exposed to? For
example those that appear in Electronic Prescribing records, Patient Medication Record or other
Information technology programs?
17. Do you think the inclusion of an audio alert affect other workflows within the department positively or
negatively?
18. Would you recommend that this technology adopt the audio alert approach seen in this study? And
why?
19. The noticeable change to this study was the inclusion of an audio alert. Do you recall any other?
differences between this study and the previous study, conducted last year, for example, implementation,
education and training etc. or can you remember?
20. Can you recall whose idea was it to implement the sound notification?

Appendix 7.0: Chapter seven survey questions

The Safe Purchase of Medicines Online: An Anonymous General Public Health Survey

Data suggests that many online pharmacies around the world are operating illegally. Many of these pharmacies sell fake or poor-quality medicines, many others may be failing to provide adequate patient information. This compromises patient safety. This study is being conducted by researchers at Keele University and the University of Oxford.

You have been invited to take part in this anonymous survey because you are a member of the general public that uses the internet. It does not matter if you have or have not purchased medicines online, you can still contribute. We would like you to complete this survey to help us understand more about three key issues which relate to online medicine purchases.

1. What would motivate you to buy medicines online?
2. What do you know about obtaining medicines safely?
3. What is your opinion on mobile phone apps which verify the status of a medicine, delivering education about buying medicines online and also providing healthcare advice?

Our research team is eager to hear your perspectives on these topics. Please take your time to answer this survey honestly. Completing this

survey should take less than 10 minutes and will help our team to understand more about key issues relating to online medicine purchases. Participation in this survey is optional.

This is an anonymous survey and will be used for academic purposes only. The outcomes of this research will be published in a peer-reviewed journal to ensure this learning is shared with fellow researchers. Your data will be stored according to Keele University data handling policy. A layperson summary will also be distributed through the same mediums used to recruit participants.

If you have any concerns about this study, please feel free to contact the lead researcher at b.naughton@keele.ac.uk. They will respond to your questions or concerns within 3 working days.

Consent

I understand that my participation is voluntary. However, once this survey is completed it will not be possible to withdraw at any time because my responses will be stored anonymously. I understand that research data collected during the study may be looked at by designated individuals from Keele University or the University of Oxford where it is relevant. By taking part in this study, I give permission for these individuals to access the data contained within my survey response. I understand that this project has been reviewed by, and received ethics clearance through, the Keele University Research Ethics Committee. I understand who will have

access to the data I provide and that this data will be stored according to Keele University data handling policy. I understand how this research will be written up and published. I understand how to raise a concern or make a complaint.

1. Considering the statements above do you consent to participate in this study? *

Mark only one oval.

Yes

No

The Extent of the Problem

2. What percentage of online pharmacies do you think operate illegally? *
Mark only one oval.

Less than 5%
6-10%
11-20%
21-30%
31-40%
41-50%
51-60%
61-70%
71-80%
81-90%
91-100%

3. Studies show that up to 97% of online pharmacies are operating illegally, are you surprised by this figure? *
Mark only one oval.

Yes
No

Demographic Questions

This section is designed to gather information about the participants of this study. This will help us to learn about the general level of education around medicine purchase, the types of people who buy medicines online, and where online medicine purchasing is most common.

4. What is your age? *
Mark only one oval.

0 - 12
13 - 15
16 - 18
19 - 24
25 - 29
30 - 39
40 - 44
45 - 49
50 - 59
60 - 69
70 - 79
80 - 89
90 - 100
Over 100

5. What is your gender? *
Mark only one oval.

Male
Female
Other (please state below)

Other:

6. What is your level of education? *
Mark only one oval.

I have a Primary School education
I have a Secondary School education
I have an Undergraduate Degree
I have a Postgraduate Degree
I have a PhD

Other:

7. What is your employment status? *
Mark only one oval.

Full-time employed
Part-time employed
Unemployed
Part-time Student

Full-time Student

8. How do you pay for your healthcare? *
Mark only one oval.

I have health insurance
Healthcare is free in my country
My country does not provide free healthcare and I do not have health insurance, I pay
for my healthcare myself when needed

9. What is your ethnic origin? *
Mark only one oval.

British White
White - Irish
Irish Traveller
Gypsy or Traveller
Other White background
Black or Black British - Caribbean
Black or Black British - African
Other Black background
Asian or Asian British - Indian
Asian or Asian British - Pakistani
Asian or Asian British - Bangladeshi
Chinese
Other Asian background
Mixed - White and Black Caribbean
Mixed - White and Black African
Mixed - White and Asian
Other mixed background
Other ethnic background
Not known
Information refused

10. What is your country of nationality? *

Mark only one oval.

(List of all countries)

11. Where do you currently live? *
Mark only one oval.

(List of all countries)
12. If you are from the United Kingdom or the US please state the first two or three figures of your postcode or zip code below, this will allow us to compare different regions of the UK and US in terms of medicines purchased online. e.g. Liverpool might be L5, Oxford might be OX1 or 100 might be New York. *

Knowledge Relating to the Safe Supply of Medicines
This section aims to understand your knowledge on the subject of "Safe Medicine Supply"

13. Do you know what a prescription is? *
Mark only one oval.

Yes
No
Not sure

14. Do you think you always need to see the doctor to get a prescription? *
Mark only one oval.

Yes
No
Not sure

15. Who else can write legal prescriptions? *
16. Who do you think is legally permitted to supply you with medicines in your country? *
17. Could you explain what you think a prescription is used for? *

18. Do you think that all medicines require a prescription? *
Mark only one oval.

Yes
No

Not sure

19. Did you know that some medicines can be bought from a supermarket, some can be bought from a pharmacist without a prescription and some must always be obtained with a prescription? *
Mark only one oval.

Yes
No

20. Why do you think there are restrictions on the sale of medicines and why some require a prescription and some do not? *
21. Would you consider buying a medicine online? (This includes any medicine e.g.
creams, ointments, injections, tablets, capsules, liquids, suspensions, inhalers, eye
drops, ear drops etc.) *
Mark only one oval.

Yes
No

22. On a scale of 1 to 10 (with 1 being unlikely and 10 being highly likely), how likely are you to buy a medicine online? *
Mark only one oval.

1 2 3 4 5 6 7 8 910

23. Have you ever purchased medicines online? (This includes any medicine e.g. creams,
inhalers, tablets, injections etc. which you requested and paid for online) *
Mark only one oval.

Yes
No (Skip to question 38).

Medicines Purchased Online

In this section, we would like to understand more about the behaviour associated with buying medicines online. Please think about a time or times that you bought medicine online.

24. Do you normally buy medicines online for yourself, your partner, a friend or a relative?
*
Mark only one oval.

Myself

My partner

A friend

A relative

I have never bought medicine online

25. What medicines are you most likely to buy online? (select option or options that apply)
Tick all that apply.

Those for cosmetic conditions e.g. hair loss, weight loss or erectile dysfunction for
example those with a long-term condition e.g. diabetes, asthma, arthritis or blood pressure control. Those with a short-term condition e.g. pain relief or antibiotics for an infection
Other:

26. What devise did or do you use to buy the medicine online? *
Mark only one oval.

A smartphone

A tablet

A laptop

A desktop computer

Asked someone else to buy them for you online

27. Please, could you describe the medicine(s) or type of medicine(s) you purchased? *
28. What were the reasons for you buying your medicine online? (please select the option
or options which apply) *
Tick all that apply.

Physically unable to get to a pharmacy
Buying medicine online is cheaper
I have to wait too long to get an appointment with my doctor
Buying medicine online is more convenient
I was embarrassed about my condition
I do not have health care provided by the state or health insurance, and cannot afford medicine from the local pharmacy
Other:

29. At any point in the process did you think the drug(s) you were buying

might be fake,
counterfeit or of poor quality? *
Mark only one oval.

Yes
No
Maybe

Other:

30. Were you asked for a prescription? *
Mark only one oval.

Yes
No
I cannot remember
Other:

31. Were you asked medical questions about your condition? *
Mark only one oval.

Yes
No
Other:

32. Did you, or the person that these medicines were bought for, take these medicines? *
Mark only one oval.
Yes
No After the last question in this section (skip to question 35).
I am not sure After the last question in this section (skip to question 35).

33. Did you or the person that these medicines were bought for think that the medicines bought online resulted in any side-effects which were different from usual? *
Mark only one oval.

Yes No, After the last question in this section, skip to question 35.
Not sure After the last question in this section, skip to question 35.

34. If you believe the medicine caused side effects, could you explain what these were? *
35. At any stage were you ever concerned that the product(s) you were buying may have been fake, falsified, substandard or of poor quality? *
Mark only one oval.

Yes
No

36. What measures, if any, did or do you take, to make sure the website that you are buying from is or was safe? *
37. What measures, if any, do you take, to make sure the medicine(s) you received was safe? *

Mobile Phone Apps for Medicine Verification

Mobile phones will soon be used by patients to verify whether or not their medicine is legitimate. This section hopes to gather your opinion on these app-based solutions, using a specific example created by Keele University School of Pharmacy.

Smartphone app demonstration: Please watch this short video of someone using an app which has been developed to help patients verify whether or not their medicines are legitimate. Once the video is finished, please answer the questions below. (A link to a YouTube video showing the app being demonstrated will be placed below)

http://youtube.com/watch?
v=DqF6B6DvHzs

38. If a mobile phone app was available as above, that could tell you whether or not your medicine was legitimate, simply by scanning the medicine when it arrived, would you use it? *
Mark only one oval.

Yes
No
Maybe

39. On a scale of 1 to 10, how useful do you think this app is, with 1 representing not useful and 10 representing very useful? *
Mark only one oval.

1 2 3 4 5 6 7 8 910

40. What do you like about the app? *
41. What don't you like about the app? *
42. Would you be happy to scan your medicine when you received it (from your community pharmacy or online) to understand if the medicine was legitimate and to learn more about your medicine? *
Mark only one oval.

Yes
No
Other:

43. What do you think needs to be in place to support or encourage you to use an app like this?

44. What would be the main barrier to you using this app? *
Mark only one oval.

I do not have a smartphone
I do not have access to a good quality internet connection
I do not have time to scan my medicines
I am not concerned about the risks of buying medicines online
I do not see any barriers

Other:

45. Why might an app like this work well or not? Please think about your specific context
i.e. your personal circumstances, local factors or surroundings.
46. These apps have the potential to capture drug details, scanning location and personal data. Which of the following organisations would you be most happy to share this data with?
Mark only one oval.

A University
A Hospital
A Private Company that owns the app
A Pharmaceutical Company

47. When you scan a drug, the drug details and the geographical location of the scan is recorded. Would you be happy to share this data with a University for research relating to "fake" or falsified drug detection? *
Mark only one oval.

Yes
No
Only if I was provided with an incentive such as healthcare advice, tailored to me
Only if I was provided with some type of financial reward or benefit

48. When you scan a drug, the drug details and the geographical location of the scan is recorded. Would you be happy to share this with a legitimate Pharmaceutical
Company? (This data would be used by the pharmaceutical company to understand
more about their products) *
Mark only one oval.
Yes
No
Only if I was provided with an incentive such as free healthcare advice, tailored to me
Only if I was provided with some type of financial reward or benefit

49. Would you be willing to share your health data with a University for research purposes? *
Mark only one oval.

Yes
No
Only if I am getting something in return

50. Would you be willing to share your health data with a Pharmaceutical Company to help them learn more about their products? *
Mark only one oval.

Yes
No
Only if I am getting something in return