BMJ Open

THE EFFECTIVENESS OF MEDICINE AUTHENTICATION TECHNOLOGY TO DETECT COUNTERFEIT, RECALLED AND EXPIRED MEDICINES: A TWO STAGE QUANTITATIVE SECONDARY CARE STUDY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013837
Article Type:	Research
Date Submitted by the Author:	10-Aug-2016
Complete List of Authors:	Naughton, Bernard; Keele University School of Pharmacy; University of Oxford, Said Buisness School Roberts, Lindsey; Academic Health Science Network, Medicines Optimisation Dopson, Sue; University of Oxford, Said Business School Chapman, Stephen; Keele University, Medicines Management Brindley, David; University of Oxford, Paediatrics; University of Oxford, Said Buisness School
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Public health, Health informatics
Keywords:	PUBLIC HEALTH, MEDICAL INFORMATICS, HEALTH POLICY, COUNTERFEIT DRUGS

THE EFFECTIVENESS OF MEDICINE AUTHENTICATION TECHNOLOGY TO DETECT COUNTERFEIT, RECALLED AND EXPIRED MEDICINES: A TWO STAGE QUANTITATIVE SECONDARY CARE STUDY

Naughton, Bernard (Doctoral Researcher) 1, 2, 3. Roberts Lindsey (Medicines Optimisation Network Manager) 4. Sue Dopson (Rhodes Trust Professor of Organisational Behavour) 2. Chapman Stephen. (Professor of Prescribing Studies) 1,5. Brindley, David (Senior Research Fellow in Healthcare Translation) 2, 5-9.

1. Institute of Science and Technology in Medicine, Keele University, Stoke-on-Trent, UK.
2. Said Business School, University of Oxford, Oxford, UK.
3. Pharmacy Department, Oxford University Hospitals NHS Trust, Oxford, UK
4. Medicines Optimisation Clinical Network, Oxford Academic Health Science Network (AHSN), Oxford, UK.
5. Department of Pediatrics, University of Oxford, Oxford, UK.
6. The Oxford – UCL Centre for the Advancement of Sustainable Medical Innovation (CASMI), University of Oxford, Oxford, UK.
7. Centre for Behavioral Medicine, UCL School of Pharmacy, University College London, London, UK.
8. Harvard Stem Cell Institute, Cambridge, MA, USA.
9. USCF-Stanford Centre of Excellence in Regulatory Science and Innovation (CERSI), USA.

Author for correspondence: Bernard David Naughton, Said Business School, Oxford University, Park End Street, Oxford OX1 1 HP, bernard.naughton@sbs.ox.ac.uk, 0044(0)1865 614995.

Keywords: Counterfeit drugs, Public Health, Health Policy, Medical Informatics

Word count =4021

ABSTRACT

EU and US regulation has been introduced to safeguard patients and improve the quality of medicines internationally. This study identifies the authentication rate and detection rate of serialised medicines using medicines authentication technology in a large UK NHS teaching hospital.

4,192 serialised medicines were authenticated over two separate eight week stages. Medicines were authenticated using secure external database cross checking, triggered by the scanning of a 2D data matrix with a unit specific 12-digit serial code as per the falsified medicines directive requirements. 4% of medicines included were pre-programmed with a message to identify the product as either expired, pack recalled, product recalled or counterfeit.

The detection rate of counterfeit, recalled and expired medicines as a combined group was 52.2% (stage one) and 53.4% (stage two). 31.8% of counterfeit medicines, 58% of recalled drugs and 64% of expired medicines were detected as a proportion of those entered into the study. The technology's technical detection rate (TDR) was 100% , however not all medicines were scanned and of those that were scanned not all that generated a warning message were appropriately quarantined. Response rates (RR) of 152 milliseconds (stage one) and 165 milliseconds (stage two) were recorded meeting the FMD mandated 300 millisecond limit.

TDR's and RR's were not a limiting factor in this study. The suboptimal detection rate of this approach is a reflection on operator compliance, which poses significant quality and safety issues with this detection approach. There is a need for further qualitative research to establish the reasons for less than absolute authentication and detection rates in the hospital environment to improve this technology in preparation for the incumbent EU and US regulative deadlines.

STRENGTHS AND LIMITATIONS

- This is the first study to academically assess the effectiveness of medicines authentication technology in the secondary care setting, demonstrating the current strengths and weaknesses of this technology, both technical and operational, for consideration by healthcare providers and policy makers
- This study is based on over 4,547 data points
- Due to the lack of widespread serialization this study required the manual adherence of 2D labels to each product, which made it possible to assess only one NHS hospital teaching hospital at the outset
- This pilot introduced 2D data matrices into an NHS hospital which were pre-programmed with counterfeit medicine alerts. This study did not introduce any counterfeit medicines into the supply chain, as to do so would be unethical

INTRODUCTION

According to the pharmaceutical security institute, between 2011 and 2015 the global incidence of drug counterfeiting has increased by 51%, with 2015 seeing the highest levels of counterfeiting to date, a 38% increase when compared to 2014(1). This upward trend can also be seen in the UK supply chain, where 11 cases of falsified medicines were detected over an 11year period (2001-2011)(2) The direct results of medicine counterfeiting include deterioration of medicine quality and therefore patient health, unnecessary drug side-effects, and death in some of the most vulnerable patient groups(3) (4) (5) (6) (7) (8) (9) (10). The indirect effects of drug counterfeiting include a loss in government tax revenue and the funding of illegal activity which may include terrorist organizations (11). High profile cases of counterfeit medicines include anti-cancer agents such as Avastin® (Bevacuzimab) (US)(4), Herceptin® (Traztuzumab) (UK, Finland and Germany)(6) and epidemic cases such as those seen in Bangladesh, where unsafe levels of ethylene glycol found in paracetamol elixir, which were responsible for the renal failure and death of over 50 patients (mostly children)(8), and represents an international medicines safety issue.

The current methods for detecting counterfeit medicine are varied in nature 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. Advancing technology has made techniques available which include spectroscopy, chromatography, SMS, hand held or portable laboratories, radiofrequency identification and serialisation (12). 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. In terms of the FMD, the term 'authentication' relates to the final scanning of a medicine and the subsequent decommissioning of a product at the point of supply to the patient to ensure authenticity. The 2011 FMD(13) (14) (15) (16) and the 2013 DQSA(17) have adopted the serialisation and verification approach for counterfeit medicine detection. This 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 whilst the DQSA 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, have not been academically assessed

and may prove difficult to implement, especially in the heterogeneous secondary care environment(18).

METHODS

Objectives

Primary Objective

To identify the Operational Authentication Rate (OAR,) Technical Detection Rate (TDR) and Operational Detection rates (ODR1 and ODR2) 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 Response Rate RR for this study.

Study Site

The district general hospital involved in this study is one of four hospitals in a large UK national health service foundation trust. 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.

Sample Selection

Medicines were selected using a set of inclusion and exclusion criteria (figure 1.0). These criteria ensured that the medicines selected for inclusion, reflected the categories of medicines governed by the FMD and the most commonly counterfeited drug groups, which included the top 50 medicines by turnover and the top 50 medicines by cost. 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.

The approach taken to identify a study drug sample resulted in a diversity of medicines representing major clinical indications and formulations (appendix 1.0). This ensured that a variety of products of differing clinical indication, formulation and cost were included in this study to represent the variety of medicines used in the secondary care environment and to avoid the inclusion of medicines which are not governed by FMD legislation. An exception was made for a number of high volume P and GSL medicines in an effort to maintain high 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 1.0: Inclusion and exclusion criteria for study medications.

Materials

Unique 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 a excel spreadsheet. The authentication technology had previously been integrated into the hospital patient medication record (PMR). The aforementioned software was operated by an existing computer terminal. The medicine codes were presented as a 2D data matrix and scanned using a hand held, terminal powered, barcode scanner, which identified the product as either 'Authenticated elsewhere' (counterfeit), 'Item Expired', 'Item Recalled (product or batch)' 'Authenticated' or 'Already Authenticated here' (figure 2.0 and 3.0).

Labeling procedure

Each 2D barcode was detailed in a excel database. Drug details such as product name, form, strength, pack size and the date in which the product was labeled were recorded in the database when the adhesive code was adhered to each study product, 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 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 7am and 2pm weekly, which maintained the serialisation of product lines throughout the study. 96% of medicines labeled, once authenticated by the operator would provide a 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 2.0). This was useful when dealing with multiple authentications of split pack medicines. Both 'Authenticated' and 'Already Authenticated here' messaging did not require quarantine (figure 2.0). A one percent subgroup of medicines were labeled with a 2D data-matrix which prompted a response of 'Authenticated elsewhere' (figure 3.0) 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 pack, recalled product and expired product at a frequency of one percent per subgroup (figure 3.0). All study products which were labeled 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 was based on the World Health Organisation (WHO) estimate that approximately 1% of the worlds medicines are counterfeit(19). To ensure equity amongst subgroups the expired medicine and recalled medicines groups were also allocated a 1% distribution.

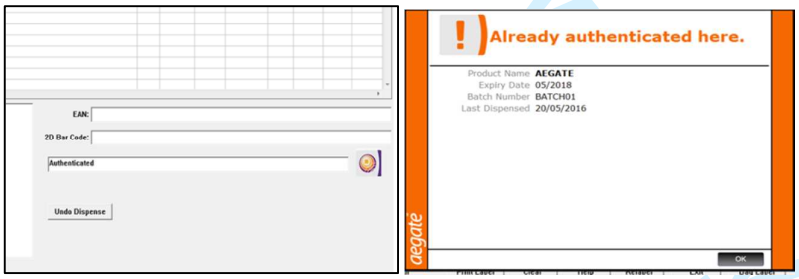


Figure 2.0: Pop-up messages triggered upon authentication of medicines that are safe for administration.

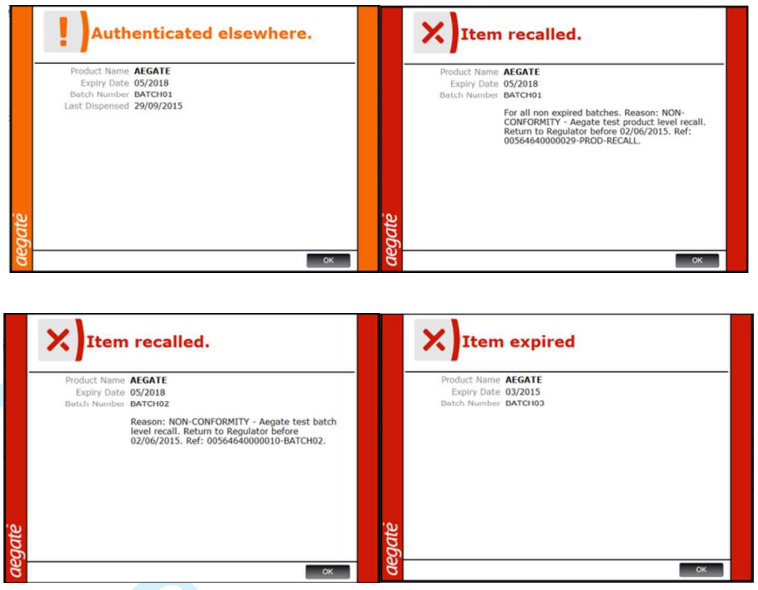


Figure 3.0: Pop-up messages triggered upon authentication of medicines requiring quarantine.

Study Design

A two week pilot stage 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 stages. 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).

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. This form was independently verified by a separate researcher to confirm results.

Statistical Analysis

Drug sample size studies were conducted to ensure the total sample of study drugs was large enough to obtain reasonable confidence intervals and margins of error using two independent sample size calculators(20) (21). 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). Z tests by proportion for independent groups(22) were employed to identify if there was

statistically significant differences between results in stage one and stage two(19). Percentages were employed to demonstrate differences between groups, which accounted for the slightly different numbers of study drugs in each stage.

Operator Groups

Stage one contained a selection of pharmacists and accredited checking technicians. Stage 2 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. 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. No one person was permitted to be involved in both stages for the same prescription according to hospital policy.

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 'suspicious/counterfeit', expired or recalled.

Researcher: Was not blinded at the point of labeling.

As authentication was performed towards the later stages of 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.

Patient Involvement

Patients, carers or lay persons 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 initially via internal presentation and via access to the research manuscript once available. Participants have been acknowledged in this publication.

RESULTS

n= Number of products entered into the study containing error messages

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

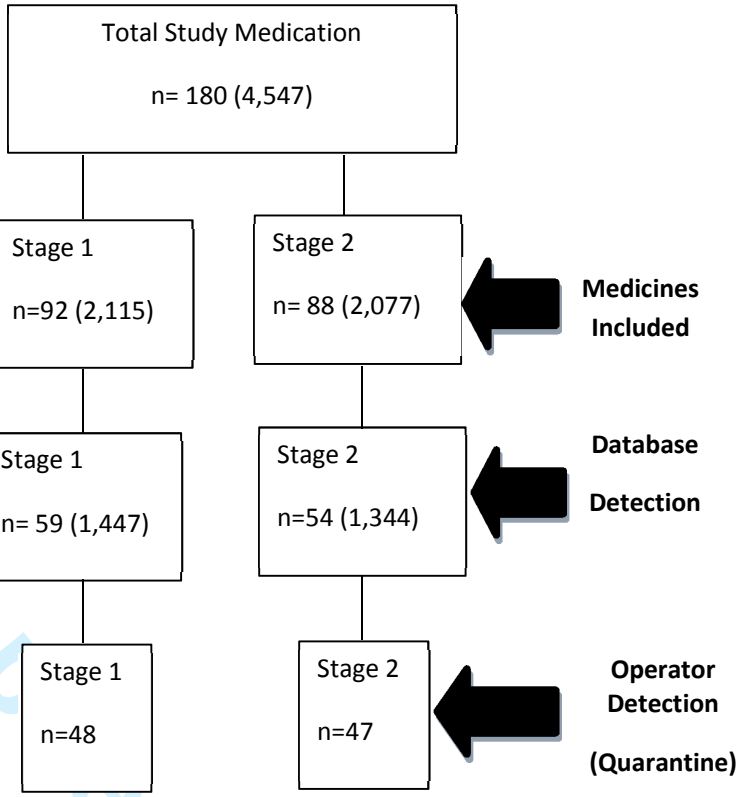
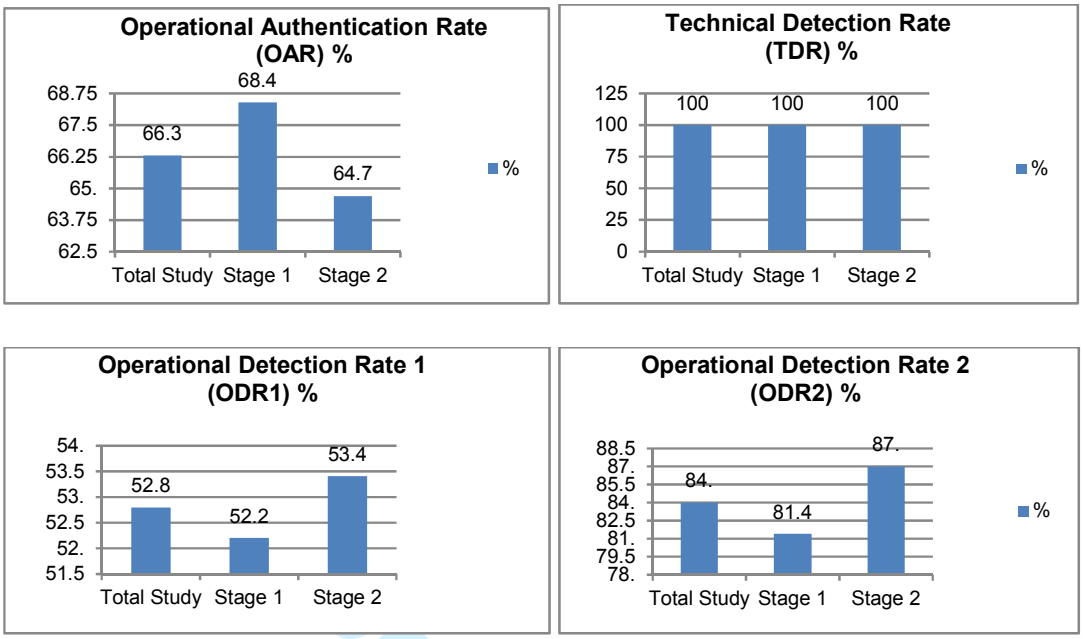


Figure 4.0 : Data tree which identified the total number of medicines serialised for each stage of the study (medicines included), medicines detected by the authentication technology, stored on the secure database (database detection) and finally, the total number of medicines in each stage quarantined for researcher investigation (operator detection).

A total of 4,547 drugs were entered into this study, (2,115=stage one; 2,077=stage two) 180 of which contained a pre-programmed message popup which described the product as either counterfeit, expired or recalled and requiring quarantine (92 =stage one, 88 = stage two)(figure 4.0). 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.



	OAR %	TDR %	ODR1%	ODR2%
Total Study	66.3	100	52.8	84
Stage 1	68.4	100	52.2	81.4
Stage 2	64.7	100	53.4	87

Figure 5.0: Graphic and numerical representation of OAR, TDR, ODR1 and ODR2 percentages.

The operational authentication rate (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% (95% CI) (stage one) and 64.7% (95% CI) (Stage two). The technical detection rate relates to the ability of the technology alone to detect counterfeit, expired or recalled medicines, i.e. read the 2D data matrix of a counterfeit drug and generate a message to identify it as such, and to store the relevant information. Multisite testing in this study has generated a 100% technical detection rate. Operational detection rate one (ODR1) 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 heterogeneous environment that the technology operated within. Only 95 (52.8%, 95 CI) of the 180 medicines requiring quarantine were quarantined, 48 (52.3%, 95% CI) in stage one and 47 (53.4%, 95% CI) in stage two. This demonstrates a difference of 1.2% between the groups. Operational detection rate two (ODR2) demonstrates the relationship between medicines identified as counterfeit, recalled or expired by the technology and those correctly quarantined by the staff. The ODR2 was 84% across both groups, 81.4 % (stage one) and 87% (stage two), a 5.6% difference between the groups.

Table 1.0: Breakdown of medicine subgroups and detection throughout the dispensing cycle.

Medicines Included	Authenticated elsewhere(Counterfeit)	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, Counterfeit 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 counterfeit medicines, 58% of recalled drugs (product and batch) and 64% of expired medicines were detected (ODR1).

Table 2.0: Z-test outcomes for ODR1 in each subgroup.

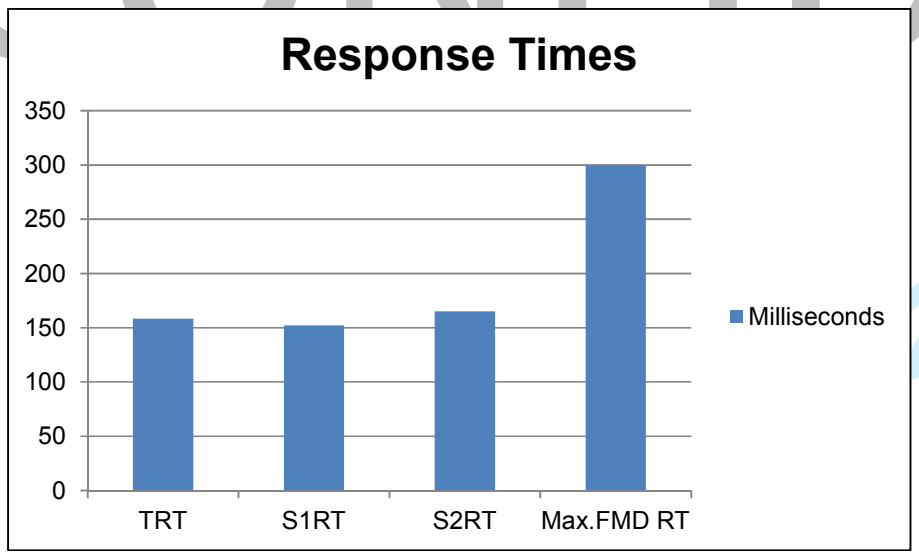
Subgroup	Counterfeit (Authenticated Elsewhere)	Pack Recalled	Expired	Product Recalled
Counterfeit (Authenticated Elsewhere)		Yes	Yes	Yes
Pack Recalled	Yes		No	No
Expired	Yes	No		No
Product	Yes	No	No	

Recalled				

Z tests by proportion for independent groups identified if the differences between ODR1 in each subgroup were of statistical significance (Yes/No outcomes were generated using table 1.0 data). The only statistical difference lied between the counterfeit group and all other subgroups, both individually and as an entire group (22).

Figure 6.0: Pop up message warnings which are generated when a counterfeit medicine (Left) and a medicine which has already been authenticated on site (right) are scanned.

The difference between alerts used for potentially counterfeit drugs (authenticated elsewhere) and the alert for medicines which have already been authenticated on site appear similar in this study.



Graph 1.0: Total response times for each stage.

The medicines authentication technology response rate (RR) is the total time taken for the information scanned from the2D 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 stage one and 165 milliseconds in stage two. The FMD mandated response rate is less than 300 milliseconds(13).

DISCUSSION

Medicines were entered into an active secondary care dispensary system. The data generated (figures 4.0 and 5.0) identified a gap between serialized 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 by the technology and those separated for quarantine (ODR2) (figure 4.0). 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 (23) (24) and the lead time to legal compliance. The OAR demonstrated a statistically significant difference of 3.7% (Z-test) (95% CI)(22) 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 better suited in terms of 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, or may have been due to a number of organizational behaviour, human and organisational factors associated with the point of authentication, in the medicine supply process. However, further investigation would be required to support this argument further.

There were no concerns raised during this study regarding the technical detection rate (figure 5.0); furthermore, this technology has been subsequently integrated and tested in a further two hospital trust sites demonstrating the same 100% detection rate. Stage one data demonstrated an ODR1 lower than stage two, however a difference of 1.2% relating to sample sizes of 59 (stage one) and 54 (stage two) was identified by z –test as non-significant 95% CI)(22), and therefore, it would not be accurate to describe a superior group in this instance. It was observed that even when the technology identified a drug to be counterfeit, recalled or expired the staff across both stages did not always quarantine that medicine. ODR2 rates (which represent the number of medicines quarantined by the operator as a percentage of those identified by the technology) demonstrated a 5.6% difference between stages, however like ODR1 rates there was not a statistical difference

between the groups, and therefore one group could not be described as 'better' than another in this study .(Z-test)(95% CI)(22). Despite the lack of statistical significance between groups there is a clinical and statistical significant difference (z-test) (95% CI)(22) between the overall group in terms of ODR1 and ODR2 compared to the expected legislative detection rate of 100% (Table 1.0 and 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 counterfeit, recalled or expired (ODR2).

There were a total of 92 (stage one) and 88 (stage two) medicines, containing quarantine messaging, introduced into this study (figure 4.0). These figures included a collection of medicines which varied in their pre-programmed messages to include; authenticated elsewhere (counterfeit), product recalled, batch recalled and item expired (table 1.0). Across both stages 31.8% of counterfeit medicines, 58% of recalled drugs and 64% of expired medicines were detected (table 1.0). There is no demonstrable difference between stage one and two for any of the subgroups in table 1.0. As a total group however, there is a difference between the ODR1 rates for the 'Authenticated Elsewhere' subgroup (31.8%) and those of other subgroups (60%) (Z-test)(95 CI)(22) (Table 2.0). 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 (orange) (figure 6.0), 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 was 152 milliseconds (stage 1) and 165 milliseconds (stage 2) (figure 6.0) demonstrable in this study over 2,791 scans, which is appropriate for systematic verification and or authentication of medicines when compared to the accepted FMD regulatory limit of 300milliseconds (13) (14). This data is however based on a relatively small sample and may not necessarily be repeated in the presence of a larger throughput. This response rate would require regular assessment once this technology is implemented nationally and internationally.

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.

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 (25). 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(23,24). 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. An accomplishment which to this day is yet to be complete across all NHS trusts. It is important to understand the role that context plays in healthcare innovation. Each hospital will have different contexts which will affect innovative implementation and it is important to understand internal and external contexts and how they that facilitate or negate the successful implementation of this healthcare technology (26) (27). It is important for policy and key decision makers to be cognizant of study results and past projects and build on what is known when planning the implementation of this detection tool; to put in place effective strategies for education and training as well as safeguards which may facilitate the authentication, and therefore, detection of counterfeit, recalled and expired medicines.

This study involved the presentation and the dissemination of a protocol to the participants. Carthy et. al., (28) 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 be realistic about the introduction of emerging technology into a heterogeneous environment(18) and to involve staff members in the implementation of projects to identify areas for improvement before legal compliance. This research aims to inform policy makers and healthcare professionals of the positive attributes and possible pitfalls of medicines authentication as a detection technology.

Further Research

Medicines authentication technology is an approach which aims to safeguard EU and US citizens against the poor quality medicines. It is important to identify the shortfalls of this technology and make improvements before the EU (2019) and US (2023) regulative deadlines. Further qualitative research is required to understand expert opinion on medicines authentication to identify

contextual reasons for less than optimum authentication and detection rates. It would also be important to understand the technological, process, educational adjustments required to improve the authentication and detection rates demonstrated in this study which in turn would improve patient safety. As research in this field moves closer to patient participation, It will be important to include patients, carers and lay persons in the design of future studies.

ACKNOWLEDGMENTS

The Oxfordshire AHSN (Gary Ford and Nick Scott Ram), Keele University and the University of Oxford. The staff at OUHFT and especially the Horton Hospital Pharmacy department team, Emma Pullan, Chief Pharmacist, Bhulesh Vadher and the Said business school for their cooperation in this initiative. Aegate ltd.,(Paul Thomas, Adrian Hicken, Peter Fox and Graham Smith) for providing the authentication software, Bedford ltd for technical IT advice, Domino ltd for providing the serialised adhesive 2D data matrices used in this study.

We wish to express our sincere thanks to the following organizations that have contributed to the CASMI Translational Stem Cell Consortium (CTSCC) as funding and events partners, without whom the consortium and the benefits it will bring to stem cell translation would be constrained: GE Healthcare, CCRM, Sartorius Stedim Biotech (formerly TAP Biosystems), Lonza, CIRM, SENS Research Foundation, UK Cell Therapy Catapult, NIH Centre for Regenerative Medicine, NYSCF, ThermoFisher Scientific, Eisai, Medipost (US), Medipost (Korea), Celgene, Roche and Oxford Biomedica. D.A.B. gratefully acknowledges personal funding from the Oxford Musculoskeletal NIHR BRU, the Said Foundation and the SENS Research Foundation.

FUNDING

This study was funded by Keele University, Oxford University and Aegate Limited. The commercial funding source provider did not play a role in the design, execution, data analysis or decision to publish. The commercial funding source did however contribute ad hoc technical advice as required.

ETHICS

Ethical approval was not required for this study as it was undertaken as a service evaluation project according to the UK health research authority guidelines.

ADITIONAL DATA

To request additional data regarding the study protocol and raw data please contact the corresponding author.

DATA SHARING

Study protocol and original research data is available upon request for academic purposes. Please contact the corresponding author for further information.

CONTRIBUTION STATEMENT

BN and DB were responsible for study conception, BN, DB, LR, SD and SC were responsible for planning, BN was responsible for data collection, data analysis and scripting. BN, DB, LR, SD and SC were responsible for the reviewing of this manuscript.

COMPETING INTERISTS

The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers. D.A.B is an employee and/or stockholders in Aegate Ltd (Melbourn, UK) that is a provider of medicines authentication services. D.A.B. is also a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK) and IP asset ventures. D.A.B. is subject to the CFA Institute's Codes, Standards, and Guidelines, and as such, this author must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation. B.N is currently not, but has previously been a consultant of Aegate limited. Additionally, at time of publication, D.A.B. and the organizations with which he is affiliated may or may not have agreed and/or pending funding commitments from the organizations named herein.

SUPPLEMENTARY APPENDICES

Appendix 1.0: Total portfolio of medicines included in study.

Value	Transaction
Afatanib 40mg injection	Paracetamol 500mg tablets
Aflibercept injection	Codeine 30mg tablets
Bosutinib 500mg injection	Omeprazole 20mg capsules
Botulinum toxin type A injection	Prednisolone 5mg tablets
Darbopoetin alpha 300mcg injection	Co-amoxiclav 625mg tablets
Dexamethasone 2mg tabs	Macrogol sachets
Ferric Carboxymaltose injection	Lactulose 300ml liquid
Infliximab 100mg infusion	Dalteparin 5000 units syringe
Lenolidamide 10mg tablets	Aspirin 75mg tablets
Lenolidamide 25mg tablets	Ibuprofen 400mg tablets
Linezolid 600mg tablets	Pipperacillin/Tazobactam 4.5g injection
Pomalidamide tablets	Adcal d3 tablets
Rivaraxiban 15mg tablets	Salbutamol inhaler 100mcg
Traztuzumab 600mg injection	Morphine Sulphate 10mg/5ml solution
Pentosan polysulphate 100mg capsules	Tramadol 50mg capsules

Table 1.0: lists the top 15 products by value and top 15 products by transaction, extracted from the initial sample of 87 products.

Bibliography

1. PSI-Inc.org [Internet]. [cited 2016 Jun 9]. Available from: http://www.psi-inc.org/incidentTrends.cfm

2. Almuzaini T, Sammons H, Choonara I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). BMJ Open. 2013 Jul;3(7):e002924.

3. Snapshot [Internet]. [cited 2016 Jun 9]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm291960.htm

4. Research C for DE and. Drug Safety and Availability - Counterfeit Version of Avastin in U.S. Distribution [Internet]. [cited 2016 Jun 9]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm291960.htm

5. Counterfeit medicines: what pharmacists should know Drug Safety Update - GOV.UK [Internet]. [cited 2016 Jun 9]. Available from: https://www.gov.uk/drug-safety-update/counterfeit-medicines-what-pharmacists-should-know

6. Fälschungen des Krebspräparats Herceptin in der EU – Schweiz nicht betroffen - Swissmedic - [Internet]. [cited 2016 Jun 9]. Available from: https://www.swissmedic.ch/aktuell/00673/02064/index.html?la

7. WHO | Growing threat from counterfeit medicines [Internet]. WHO. [cited 2016 Jun 9]. Available from: http://www.who.int/bulletin/volumes/88/4/10-020410/en/

8. 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.

9. The Effects of Falsified and Substandard Drugs - Countering the Problem of Falsified and Substandard Drugs - NCBI Bookshelf [Internet]. [cited 2016 Jun 9]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK202526/#ref_000225.

10. 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(6 Suppl):119–26.

11. Caunic I, Prelipcean G. The Market for Counterfeit Goods and Financing of the Extremist Organizations in Europe in the Last Decade. In: 2nd International Conference on Humanities, Historical and Social Sciences, IPEDR [Internet]. 2011 [cited 2016 Jun 9]. Available from: http://www.ipedr.com/vol17/65-CHHSS%202011-H10119.pdf

12. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong L, Stergachis A. Technologies for Detecting Falsified and Substandard Drugs in Low and Middle-Income Countries. Sullivan DJ, editor. PLoS ONE. 2014 Mar 26;9(3):e90601.

13. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal productsText with EEA relevance - dir_2011_62_en.pdf [Internet]. [cited 2016 Jun 9]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf

14. COMMISSION DELEGATED REGULATION (EU) 2016/ 161 - of 2 October 2015 - supplementing Directive 2001/ 83/ EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use - http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2016_032_R_0001&from=EN [Internet]. [cited 2016 Jun 9]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2016_032_R_0001&from=EN

15. Naughton BD, Smith JA, Brindley DA. Establishing good authentication practice (GAP) in secondary care to protect against falsified medicines and improve patient safety. Eur J Hosp Pharm Sci Pract. 2016 Mar;23(2):118–20.

16. Book Excerpt: Fundamentals of EU Regulatory Affairs, Seventh Edition, Chapter 8: European Union Falsified Medicines Directive: Requirements and Implications for Multi-Stakeholder Healthcare Delivery | RAPS [Internet]. [cited 2016 Jun 9]. Available from: http://www.raps.org/Regulatory-Focus/RAPS-Latest/2015/12/18/23808/Book-Excerpt-Fundamentals-of-EU-Regulatory-Affairs-Seventh-Edition-Chapter-8-European-Union-Falsified-Medicines-Directive-Requirements-and-Implications-for-Multi-Stakeholder-Healthcare-Delivery/

17. Upton F. H.R.3204 - 113th Congress (2013-2014): Drug Quality and Security Act [Internet]. 2013 [cited 2016 Jun 9]. Available from: https://www.congress.gov/bill/113th-congress/house-bill/3204

18. Naughton B, Vadher B, Smith J, Smith G, Chapman S, Dopson S, et al. EU Falsified Medicines Directive mandatory requirements for secondary care: A concise review. J Generic Med Bus J Generic Med Sect. 2015 Sep 1;12(3–4):95–101.

19. 1 - Justification - TheNewEstimatesCounterfeit.pdf [Internet]. [cited 2016 Jun 9]. Available from: http://www.who.int/medicines/services/counterfeit/impact/TheNewEstimatesCounterfeit.pdf

20. Sample Size Calculator by Raosoft, Inc. [Internet]. [cited 2016 Jun 9]. Available from: http://www.raosoft.com/samplesize.html

21. Sample Size Calculator - Confidence Level, Confidence Interval, Sample Size, Population Size, Relevant Population - Creative Research Systems [Internet]. [cited 2016 Jun 9]. Available from: http://www.surveysystem.com/sscalc.htm

22. Z-test for Proportions-Independent Groups [Internet]. McCallum Layton. [cited 2016 Jun 9]. Available from: https://www.mccallum-layton.co.uk/tools/statistic-calculators/z-test-for-proportions-independent-groups-calculator/

23. Hendy J. Challenges to implementing the national programme for information technology (NPfIT): a qualitative study. BMJ. 2005 Aug 6;331(7512):331–6.

24. Hendy J, Fulop N, Reeves BC, Hutchings A, Collin S. Implementing the NHS information technology programme: qualitative study of progress in acute trusts. BMJ. 2007 Jun 30;334(7608):1360–1360.

25. Nelson RR. QUARTERLY ExECUTIVE. 2007 [cited 2016 Jun 9]; Available from: http://www2.comm.virginia.edu/cmit/Research/MISQE%206-07.pdf

26. Dopson S, Fitzgerald L, Ferlie E. Understanding Change and Innovation in Healthcare Settings: Reconceptualizing the Active Role of Context. J Change Manag. 2008 Dec;8(3–4):213–31.

27. Robert G, Fulop N. The role of context in successful improvement. Perspect Context Sel Essays Considering Role Context Success Qual Improv Lond Health Found [Internet]. 2014 [cited 2016 Jul 4];31. Available from: http://www.health.org.uk/sites/default/files/PerspectivesOnContextRobertFulopTheRoleOfContextInSuccessfulImprovement.pdf

28. Carthey J, Walker S, Deelchand V, Vincent C, Griffiths WH. Breaking the rules: understanding non-compliance with policies and guidelines. BMJ. 2011 Sep 13;343(sep13 3):d5283–d5283.

BMJ Open

THE EFFECTIVENESS OF MEDICINE AUTHENTICATION TECHNOLOGY TO DETECT COUNTERFEIT, RECALLED AND EXPIRED MEDICINES: A TWO STAGE QUANTITATIVE SECONDARY CARE STUDY

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013837.R1
Article Type:	Research
Date Submitted by the Author:	29-Sep-2016
Complete List of Authors:	Naughton, Bernard; Keele University School of Pharmacy; University of Oxford, Said Buisness School Roberts, Lindsey; Academic Health Science Network, Medicines Optimisation Dopson, Sue; University of Oxford, Said Business School Chapman, Stephen; Keele University, Medicines Management Brindley, David; University of Oxford, Paediatrics; University of Oxford, Said Buisness School
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Public health, Health informatics
Keywords:	PUBLIC HEALTH, MEDICAL INFORMATICS, Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, COUNTERFEIT DRUGS

THE EFFECTIVENESS OF MEDICINE AUTHENTICATION TECHNOLOGY TO DETECT COUNTERFEIT, RECALLED AND EXPIRED MEDICINES: A TWO STAGE QUANTITATIVE SECONDARY CARE STUDY

Naughton, Bernard (Doctoral Researcher) 1, 2, 3. Roberts Lindsey (Medicines Optimisation Network Manager) 4. Sue Dopson (Rhodes Trust Professor of Organisational Behavior) 2. Chapman Stephen. (Professor of Prescribing Studies) 1,5. Brindley, David (Senior Research Fellow in Healthcare Translation) 2, 5-9.

1. Institute of Science and Technology in Medicine, Keele University, Stoke-on-Trent, UK.
2. Said Business School, University of Oxford, Oxford, UK.
3. Pharmacy Department, Oxford University Hospitals NHS Foundation Trust, Oxford, UK
4. Medicines Optimisation Clinical Network, Oxford Academic Health Science Network (AHSN), Oxford, UK.
5. Department of Pediatrics, University of Oxford, Oxford, UK.
6. The Oxford – UCL Centre for the Advancement of Sustainable Medical Innovation (CASMI), University of Oxford, Oxford, UK.
7. Centre for Behavioral Medicine, UCL School of Pharmacy, University College London, London, UK.
8. Harvard Stem Cell Institute, Cambridge, MA, USA.
9. USCF-Stanford Centre of Excellence in Regulatory Science and Innovation (CERSI), USA.

Author for correspondence: Bernard David Naughton, Said Business School, Oxford University, Park End Street, Oxford OX1 1 HP, bernard.naughton@sbs.ox.ac.uk, 0044(0)1865 614995.

Keywords: Counterfeit drugs, Public Health, Health Policy, Medical Informatics

Word count =4326

ABSTRACT

Objectives: To identify the authentication and detection rate of serialised medicines using medicines authentication technology.

Design and Intervention: 4,192 serialised medicines were authenticated over two separate eight week stages in 2015. Medicines were authenticated using secure external database cross checking, triggered by the scanning of a 2D data matrix with a unit specific 12-digit serial code. 4% of medicines included were pre-programmed with a message to identify the product as either expired, pack recalled, product recalled or counterfeit.

Setting: A site within a large UK NHS teaching hospital trust.

Participants: Accredited checking staff, pharmacists and dispensers in a pharmacy department.

Primary outcome measures: Authentication and detection rate of counterfeit expired and recalled medicines.

Results: The operational detection rate of counterfeit, recalled and expired medicines scanned as a combined group was 81.4% (stage one) and 87% (stage two). The technology's technical detection rate (TDR) was 100%, however not all medicines were scanned and of those that were scanned not all that generated a warning message were quarantined. Due to an operational authentication rate (OAR) of 66.3% (over both stages) only 31.8% of counterfeit medicines, 58% of recalled drugs and 64% of expired medicines were detected as a proportion of those entered into the study. Response times (RT) of 152 milliseconds (stage one) and 165 milliseconds (stage two) were recorded, meeting the falsified medicines directive (FMD) mandated 300 millisecond limit.

Conclusions: TDR's and RT's were not a limiting factor in this study. The suboptimal OAR, poses significant quality and safety issues with this detection approach. Authentication at the checking stage however demonstrated higher OAR's. There is a need for further qualitative research to establish the reasons for less than absolute authentication and detection rates in the hospital environment to improve this technology in preparation for the incumbent EU regulative deadline.

Article Summary: Strengths and Limitations

- This is the first study to academically assess the effectiveness of medicines authentication technology in the secondary care setting, demonstrating the current strengths and weaknesses of this technology, both technical and operational, for consideration by healthcare providers and policy makers.

- This study is based on the introduction of 4,192 2D data matrices into a live hospital dispensary.
- Due to the lack of widespread serialization this study required the manual adherence of 2D labels to each product, which made it possible to assess only one NHS hospital teaching hospital at the outset.
- This pilot introduced 2D data matrices into an NHS hospital which were pre-programmed with counterfeit medicine alerts. This study did not introduce any counterfeit medicines into the supply chain, as to do so would be unethical.

INTRODUCTION

The terms counterfeit and falsified are often used interchangeably. According to the food and drug administration (FDA) a counterfeit medicine is 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 (1). According to the European medicines agency falsified medicines are fake medicines that pass themselves off as real, authorised medicines (2). The pharmaceutical security institute, report that between 2011 and 2015 the global incidence of drug counterfeiting has increased by 51%, with 2015 seeing the highest levels of counterfeiting to date, a 38% increase when compared to 2014(3). This upward trend can also be seen in the UK supply chain, where 11 cases of falsified medicines were detected over an 11year period (2001-2011)(4) The direct results of medicine counterfeiting include deterioration of medicine quality and therefore patient health, unnecessary drug side-effects, and death in some of the most vulnerable patient groups(5) (6) (7) (8) (9) (10) (11) (12). The indirect effects of drug counterfeiting include a loss in government tax revenue and the funding of illegal activity which may include terrorist organizations (13). High profile cases of counterfeit medicines include anti-cancer agents such as Avastin® (Bevacuzimab) (US)(6), Herceptin® (Traztuzumab) (UK, Finland and Germany)(8) and epidemic cases such as those seen in Bangladesh, where unsafe levels of ethylene glycol found in paracetamol elixir, which were responsible for the renal failure and death of over 50 patients (mostly children)(10), and represents an international medicines safety issue.

The current methods for detecting counterfeit medicine are varied in nature and span from laboratory based methods through to SMS texting. The detection of counterfeit medicines by customs officials usually occurs as a result of intelligence or random checks, suspect medicines are then sent away for laboratory based analysis. Advancing technology has made a variety of techniques available which include spectroscopy, chromatography, SMS, hand held or portable laboratories, radiofrequency identification and serialisation (14). 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. In terms of the falsified medicines directive (FMD), the term 'authentication' relates to the final scanning of a medicine and the subsequent decommissioning of a product at the point of supply to the patient to ensure authenticity. The 2011 FMD(15) (16) (17) (18) and the 2013 drug quality and security act (DQSA) (19) have adopted the serialisation and verification approach for counterfeit medicine detection. This 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 whilst the DQSA 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, have not been academically assessed and may prove difficult to implement, especially in the heterogeneous secondary care environment(20).

OBJECTIVES

Primary Objectives

To identify the:

Operational Authentication Rate (OAR): The percentage of medicines scanned as a proportion of those entered into the study.

Technical Detection Rate (TDR): The ability of the authentication technology to read the 2D data matrix of a counterfeit drug and generate a message to identify it as such.

Operational Detection rates (ODR): The number of medicines quarantined as a percentage of those identified as recalled, expired or potentially counterfeit by the technology.

Secondary Objectives

To identify the:

Optimum point in the dispensing process to authenticate medicines based on OAR and ODR.

Response Time (RT) of the technology: The time it takes to scan a medicine, send the information to an external database for cross checking and return an accurate result.

METHODS

Study Site

The district general hospital involved in this study is one of four hospitals in a large UK National Health Service foundation trust. 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.

Sample Selection

Medicines were selected using a set of inclusion and exclusion criteria (figure 1.0). These criteria ensured that the medicines selected for inclusion, reflected the categories of medicines governed by the FMD and the most commonly counterfeited drug groups, which included the top 50 medicines by turnover and the top 50 medicines by cost. 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.

The approach taken to identify a study drug sample resulted in a diversity of medicines representing major clinical indications and formulations (appendix 1.0). This ensured that a variety of products of differing clinical indication, formulation and cost were included in this study to represent the variety of medicines used in the secondary care environment and to avoid the inclusion of medicines which are not governed by FMD legislation. An exception was made for a number of high volume pharmacy supervised sale (P) and general sales list (GSL) medicines in an effort to maintain high dispensing throughput.

Figure 1.0: Inclusion and exclusion criteria for study medications.

Materials

Unique 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 a excel spreadsheet. The authentication technology had previously been integrated into the hospital patient medication record (PMR). The aforementioned software was operated by an existing computer terminal. The medicine codes were presented as a 2D data matrix and scanned using a hand held, terminal powered, barcode scanner, which identified the product as either 'Authenticated elsewhere' (counterfeit), 'Item Expired', 'Item Recalled (product or batch)' 'Authenticated' or 'Already Authenticated here' (figure 2.0 and 3.0).

Labeling procedure

Each 2D barcode was detailed in a excel database. Drug details such as product name, form, strength, pack size and the date in which the product was labeled were recorded in the database when the adhesive code was adhered to each study product, 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 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 7am and 2pm weekly, which maintained the serialisation of product lines throughout the study. 96% of medicines labeled, once authenticated by the operator would provide a 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 2.0). This was useful when dealing with multiple authentications of split pack medicines. Both 'Authenticated' and 'Already Authenticated here' messaging did not require quarantine (figure 2.0). A one percent subgroup of medicines were labeled with a 2D data-matrix which prompted a response of 'Authenticated elsewhere' (figure 3.0) 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 pack, recalled product and expired product at a frequency of one percent per subgroup (figure 3.0). All study products which were labeled 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 was based on the World Health Organisation (WHO) estimate that approximately 1% of the worlds

medicines are counterfeit(21). To ensure equity amongst subgroups the expired medicine and recalled medicines groups were also allocated a 1% distribution.

Figure 2.0: Pop-up messages triggered upon authentication of medicines that are safe for administration.

Figure 3.0: Pop-up messages triggered upon authentication of medicines requiring quarantine.

Study Design

A two week pilot stage 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 stages. 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).

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. This form was independently verified by a separate researcher to confirm results.

Statistical Analysis

Drug sample size studies were conducted to ensure the total sample of study drugs was large enough to obtain reasonable confidence intervals and margins of error using two independent sample size calculators(22) (23). 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). Z tests by proportion for independent groups(24) were employed to identify if there was statistically significant differences between results in stage one and stage two(19). Percentages were employed to demonstrate differences between groups, which accounted for the slightly different numbers of study drugs in each stage.

Operator Groups

Stage one contained a selection of pharmacists and accredited checking technicians. Stage 2 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. 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. Staff are not however permitted to be involved in both stages for the same prescription according to hospital policy.

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 'suspicious/counterfeit', expired or recalled.

Researcher: Was not blinded at the point of labeling.

As authentication was performed towards the later stages of 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.

Patient Involvement

Patients, carers or lay persons did not participate in this research. The design of this study, the research questions and the outcome 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 initially via internal presentation and via access to the research manuscript once available. Participants have been acknowledged in this publication.

RESULTS

Figure 4.0 : Data tree which identified the total number of medicines serialised for each stage of the study (no. of medicines included), medicines detected by the authentication technology, stored on the secure database (operator authenticated) and finally, the total number of medicines in each stage quarantined for researcher investigation (operator detection).

A total of 4,192 drugs were entered into this study, (2,115=stage one; 2,077=stage two) 180 of which contained a pre-programmed message popup which described the product as counterfeit, expired or recalled and requiring quarantine (92 =stage one, 88 = stage two) (figure 4.0). 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 (ODR).

Figure 5.0: Graphic and numerical representation of OAR, TDR and ODR percentages.

The operational authentication rate (OAR) relates to the number of medicines authenticated in a particular stage as a percentage of the total number of medicines entered into said stage. For this study the OAR was 66.3% overall, 68.4% (95% CI) (stage one) and 64.7% (95% CI) (Stage two)

The technical detection rate relates to the ability of the technology alone to detect counterfeit, expired or recalled medicines, i.e. read the 2D data matrix of a counterfeit drug and generate a message to identify it as such, and to store the relevant information. Multisite testing in this study has generated a 100% technical detection rate. Operational detection rate (ODR) demonstrates the relationship between scanned medicines identified as counterfeit, recalled or expired by the technology and those correctly quarantined by the staff. The ODR across scanned medicines was 84% across all groups, 81.4 % (stage one) and 87% (stage two), a 5.6% difference between the groups. The group with the lowest ODR was the 'Authenticated elsewhere (counterfeit)' group which demonstrated a rate of 58.3%.

Table 1.0: Breakdown of data from figure 4.0 by stage and authentication technology alerts category to demonstrate detection at each step of the study.

	Authentication Technology Alert Categories			
Stages	Authenticated elsewhere(Counterfeit)	Product Recalled	Batch Recalled	Item Expired
	No. of Medicines Included			
Stage One	22	24	24	22
Stage Two	22	22	22	22
	Operator Authenticated			
Stage One	13	12	18	16
Stage Two	11	17	12	14
	Operator Detected (Quarantine)			
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, Counterfeit 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 counterfeit medicines, 58% of recalled drugs (product and batch) and 64% of expired medicines were detected as a percentage of those entered into the study.

Table 2.0: Z-test outcomes for ODR in each subgroup.

Subgroup	Counterfeit (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 of statistical significance (Yes/No outcomes were generated using table 1.0 data). The only statistical difference lied between the counterfeit group and all other subgroups, both individually and as an entire group (22).

Figure 6.0: Pop up message warnings which are generated when a counterfeit medicine (Left) and a medicine which has already been authenticated on site (right) are scanned.

The difference between alerts used for potentially counterfeit drugs (authenticated elsewhere) and the alert for medicines which have already been authenticated on site appear similar in this study.

Figure 7.0: Total response times for each stage.

The medicines authentication technology response time (RT) is the total time taken for the information scanned from the2D 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 stage one (S1) and 165 milliseconds in stage two (S2). The FMD mandated response rate is less than 300 milliseconds (15).

DISCUSSION

Medicines were entered into an active secondary care dispensary system. The data generated (figures 4.0 and 5.0) identified a gap between serialized medicines entered into the study and those authenticated by the operators, the operating authentication rate (OAR). There also appears to be a disparity between medicines identified by the technology and those separated for quarantine (ODR) (figure 4.0). 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 which may be due to operator compliance issues. The OAR demonstrated a statistically significant difference of 3.7% (Z-test) (95% CI)(24) 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 better suited in terms of 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, or may have been due to a number of organizational behavior, human and organisational factors associated with the point of authentication, in the medicine supply process. However, further investigation would be required to support this argument further.

There were no concerns raised during this study regarding the technical detection rate (figure 5.0); this technology has been subsequently integrated and tested in a further two hospital trust sites demonstrating the same 100% detection rate.

It was observed that even when the technology identified a drug to be counterfeit, recalled or expired the staff across both stages did not always quarantine that medicine. ODR rates (which represent the number of medicines quarantined by the operator as a percentage of those identified by the technology) demonstrated a 5.6% difference between stages, however there was not a statistical difference between the groups, and therefore one group could not be described as 'better' than another in this study for this parameter .(Z-test)(95% CI)(24). Despite the lack of statistical significance between groups there is a clinical and statistical significant difference (z-test) (95% CI)(24) between the overall group in terms of ODR compared to the expected legislative detection rate of 100% (Table 1.0 and 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 counterfeit, recalled or expired (ODR).

As a total group, there is a difference between the ODR rates for the 'Authenticated Elsewhere' subgroup (58.3%) and those of other subgroups (expired, recalled pack and recalled

batch, average ODR 91%) (Z-test)(95 CI)(24) (Table 2.0). 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 (orange) (figure 6.0), with the former requiring quarantine and the latter requiring no action. This issue could be alleviated by changing the colour of the 'Authenticated elsewhere' message to red which would match other pop-ups requiring medicine quarantine.

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 was 152 milliseconds (stage 1) and 165 milliseconds (stage 2) (figure 6.0) demonstrable in this study over 2,791 scans, which is appropriate for systematic verification and or authentication of medicines when compared to the accepted FMD regulatory limit of 300milliseconds (15) (16). This data is however based on a relatively small sample and may not necessarily be repeated in the presence of a larger throughput. This response rate would require regular assessment once this technology is implemented nationally and internationally.

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.

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 (25). 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(26,27). 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. An accomplishment which to this day is yet to be complete across all NHS trusts. It is important to understand the role that context plays in healthcare innovation. Each hospital will have different

contexts which will affect innovative implementation and it is important to understand internal and external contexts and how they that facilitate or negate the successful implementation of this healthcare technology (28) (25). It is important for policy and key decision makers to be cognizant of study results and past projects and build on what is known when planning the implementation of this detection tool; to put in place effective strategies for education and training as well as safeguards which may facilitate the authentication, and therefore, detection of counterfeit, recalled and expired medicines.

This study involved the presentation and the dissemination of an authentication protocol to the participants. Carthy et. al., (29) 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, perhaps a more innovative and interactive approach to education and training would facilitate a higher compliance rate. Other ways of improve compliance may include incentives. The FMD allows nations to use a reimbursement code as part of the 2D matrix which would result in payment by authentication. This would not only increase the operational authentication rate but also help to reduce fraud within the NHS. It is therefore important to be realistic about the introduction of technologies into a heterogeneous environment(20) and to involve staff members in the implementation of projects to identify areas for improvement before legal compliance.

Further Research

Medicines authentication technology is an approach which aims to safeguard EU and US citizens against the poor quality medicines. It is important to identify the shortfalls of this technology and make improvements before the EU (2019) and US (2023) regulative deadlines. Further qualitative research is required to understand expert opinion on medicines authentication to identify contextual reasons for less than optimum authentication rates and less than absolute detection rates. It would also be important to understand the technological, process and educational adjustments required to improve the authentication and detection rates demonstrated in this study which in turn would improve patient safety. As research in this field moves closer to patient participation, It will be important to include patients, carers and lay persons in the design of future studies.

Conclusions

Medicines authentication technology is capable of meeting the FMD mandated response speed of less than 300 milliseconds and demonstrates a 100% technical detection rate. The operational

authentication rate requires improvement which may be facilitated by innovative and interactive education and training or through the introduction of incentives such as 'payment by authentication'. The operator detection rate was also less than 100% and further qualitative research is required to identify technical solutions to facilitate the correct quarantine of medicines identified as recalled, expired or potentially counterfeit.

ACKNOWLEDGMENTS

The Oxfordshire AHSN (Gary Ford and Nick Scott Ram), Keele University and the University of Oxford. The staff at OUHFT and especially the Horton Hospital Pharmacy department team, Emma Pullan, Chief Pharmacist Bhulesh Vadher and the Said business school for their cooperation in this initiative. Aegate ltd.,(Paul Thomas, Adrian Hicken, Peter Fox and Graham Smith) for providing the authentication software, Bedford ltd for technical IT advice, Domino ltd for providing the serialised adhesive 2D data matrices used in this study.

We wish to express our sincere thanks to the following organizations that have contributed to the CASMI Translational Stem Cell Consortium (CTSCC) as funding and events partners, without whom the consortium and the benefits it will bring to stem cell translation would be constrained: GE Healthcare, CCRM, Sartorius Stedim Biotech (formerly TAP Biosystems), Lonza, CIRM, SENS Research Foundation, UK Cell Therapy Catapult, NIH Centre for Regenerative Medicine, NYSCF, ThermoFisher Scientific, Eisai, Medipost (US), Medipost (Korea), Celgene, Roche and Oxford Biomedica. D.A.B. gratefully acknowledges personal funding from the Oxford Musculoskeletal NIHR BRU, the Said Foundation and the SENS Research Foundation.

FUNDING

This study was funded by Keele University, Oxford University and Aegate Limited. The commercial funding source provider did not play a role in the design, execution, data analysis or decision to publish. The commercial funding source did however contribute ad hoc technical advice as required.

ETHICS

Ethical approval was not required for this study as it was undertaken as a service evaluation project according to the UK health research authority guidelines.

ADITIONAL DATA

To request additional data regarding the study protocol and raw data please contact the corresponding author.

DATA SHARING

Study protocol and original research data is available upon request for academic purposes. Please contact the corresponding author for further information.

CONTRIBUTION STATEMENT

BN and DB were responsible for study conception, BN, DB, LR, SD and SC were responsible for planning, BN was responsible for data collection, data analysis and scripting. BN, DB, LR, SD and SC were responsible for the reviewing of this manuscript.

COMPETING INTERISTS

The content outlined herein represents the individual opinions of the authors and may not necessarily represent the viewpoints of their employers. D.A.B is an employee and/or stockholders in Aegate Ltd (Melbourn, UK) that is a provider of medicines authentication services. D.A.B. is also a stockholder in Translation Ventures Ltd. (Charlbury, Oxfordshire, UK) and IP asset ventures. D.A.B. is subject to the CFA Institute's Codes, Standards, and Guidelines, and as such, this author must stress that this piece is provided for academic interest only and must not be construed in any way as an investment recommendation. B.N is currently not, but has previously been a consultant of Aegate limited. Additionally, at time of publication, D.A.B. and the organizations with which he is affiliated may or may not have agreed and/or pending funding commitments from the organizations named herein.

Bibliography:

1. Research C for DE and. Counterfeit Medicine [Internet]. [cited 2016 Sep 20]. Available from: http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/CounterfeitMedicine/

2. European Medicines Agency - Human regulatory - Falsified medicines [Internet]. [cited 2015 Jul 9]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000186.jsp

3. PSI-Inc.org [Internet]. [cited 2016 Jun 9]. Available from: http://www.psi-inc.org/incidentTrends.cfm

4. Almuzaini T, Sammons H, Choonara I. Substandard and falsified medicines in the UK: a retrospective review of drug alerts (2001–2011). BMJ Open. 2013 Jul;3(7):e002924.

5. Snapshot [Internet]. [cited 2016 Jun 9]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm291960.htm

6. Research C for DE and. Drug Safety and Availability - Counterfeit Version of Avastin in U.S. Distribution [Internet]. [cited 2016 Jun 9]. Available from: http://www.fda.gov/Drugs/DrugSafety/ucm291960.htm

7. Counterfeit medicines: what pharmacists should know Drug Safety Update - GOV.UK [Internet]. [cited 2016 Jun 9]. Available from: https://www.gov.uk/drug-safety-update/counterfeit-medicines-what-pharmacists-should-know

8. Fälschungen des Krebspräparats Herceptin in der EU – Schweiz nicht betroffen - Swissmedic - [Internet]. [cited 2016 Jun 9]. Available from: https://www.swissmedic.ch/aktuell/00673/02064/index.html?la

9. WHO | Growing threat from counterfeit medicines [Internet]. WHO. [cited 2016 Jun 9]. Available from: http://www.who.int/bulletin/volumes/88/4/10-020410/en/

10. 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.

11. The Effects of Falsified and Substandard Drugs - Countering the Problem of Falsified and Substandard Drugs - NCBI Bookshelf [Internet]. [cited 2016 Jun 9]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK202526/#ref_000225.

12. 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(6 Suppl):119–26.

13. Caunic I, Prelipcean G. The Market for Counterfeit Goods and Financing of the Extremist Organizations in Europe in the Last Decade. In: 2nd International Conference on Humanities, Historical and Social Sciences, IPEDR [Internet]. 2011 [cited 2016 Jun 9]. Available from: http://www.ipedr.com/vol17/65-CHHSS%202011-H10119.pdf

14. Kovacs S, Hawes SE, Maley SN, Mosites E, Wong L, Stergachis A. Technologies for Detecting Falsified and Substandard Drugs in Low and Middle-Income Countries. Sullivan DJ, editor. PLoS ONE. 2014 Mar 26;9(3):e90601.

15. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal productsText with EEA relevance - dir_2011_62_en.pdf [Internet]. [cited 2016 Jun 9]. Available from: http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf

16. COMMISSION DELEGATED REGULATION (EU) 2016/ 161 - of 2 October 2015 - supplementing Directive 2001/ 83/ EC of the European Parliament and of the Council by laying down detailed rules for the safety features appearing on the packaging of medicinal products for human use - http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2016_032_R_0001&from=EN [Internet]. [cited 2016 Jun 9]. Available from: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOL_2016_032_R_0001&from=EN

17. Naughton BD, Smith JA, Brindley DA. Establishing good authentication practice (GAP) in secondary care to protect against falsified medicines and improve patient safety. Eur J Hosp Pharm Sci Pract. 2016 Mar;23(2):118–20.

18. Book Excerpt: Fundamentals of EU Regulatory Affairs, Seventh Edition, Chapter 8: European Union Falsified Medicines Directive: Requirements and Implications for Multi-Stakeholder Healthcare Delivery | RAPS [Internet]. [cited 2016 Jun 9]. Available from: http://www.raps.org/Regulatory-Focus/RAPS-Latest/2015/12/18/23808/Book-Excerpt-Fundamentals-of-EU-Regulatory-Affairs-Seventh-Edition-Chapter-8-European-Union-Falsified-Medicines-Directive-Requirements-and-Implications-for-Multi-Stakeholder-Healthcare-Delivery/

19. Upton F. H.R.3204 - 113th Congress (2013-2014): Drug Quality and Security Act [Internet]. 2013 [cited 2016 Jun 9]. Available from: https://www.congress.gov/bill/113th-congress/house-bill/3204

20. Naughton B, Vadher B, Smith J, Smith G, Chapman S, Dopson S, et al. EU Falsified Medicines Directive mandatory requirements for secondary care: A concise review. J Generic Med Bus J Generic Med Sect. 2015 Sep 1;12(3–4):95–101.

21. 1 - Justification - TheNewEstimatesCounterfeit.pdf [Internet]. [cited 2016 Jun 9]. Available from: http://www.who.int/medicines/services/counterfeit/impact/TheNewEstimatesCounterfeit.pdf

22. Sample Size Calculator by Raosoft, Inc. [Internet]. [cited 2016 Jun 9]. Available from: http://www.raosoft.com/samplesize.html

23. Sample Size Calculator - Confidence Level, Confidence Interval, Sample Size, Population Size, Relevant Population - Creative Research Systems [Internet]. [cited 2016 Jun 9]. Available from: http://www.surveysystem.com/sscalc.htm

24. Z-test for Proportions-Independent Groups [Internet]. McCallum Layton. [cited 2016 Jun 9]. Available from: https://www.mccallum-layton.co.uk/tools/statistic-calculators/z-test-for-proportions-independent-groups-calculator/

25. Robert G, Fulop N. The role of context in successful improvement. Perspect Context Sel Essays Considering Role Context Success Qual Improv Lond Health Found [Internet]. 2014 [cited 2016 Jul 4];31. Available from:

http://www.health.org.uk/sites/default/files/PerspectivesOnContextRobertFulopTheRoleOfContextInSuccessfulImprovement.pdf

26. Hendy J, Fulop N, Reeves BC, Hutchings A, Collin S. Implementing the NHS information technology programme: qualitative study of progress in acute trusts. BMJ. 2007 Jun 30;334(7608):1360–1360.

27. Hendy J. Challenges to implementing the national programme for information technology (NPfIT): a qualitative study. BMJ. 2005 Aug 6;331(7512):331–6.

28. Dopson S, Fitzgerald L, Ferlie E. Understanding Change and Innovation in Healthcare Settings: Reconceptualizing the Active Role of Context. J Change Manag. 2008 Dec;8(3–4):213–31.

29. Carthey J, Walker S, Deelchand V, Vincent C, Griffiths WH. Breaking the rules: understanding non-compliance with policies and guidelines. BMJ. 2011 Sep 13;343(sep13 3):d5283–d5283.

SUPPLEMENTARY APPENDICES

Appendix 1.0: Total portfolio of medicines included in study.

Table 1.0: lists the top 15 products by value and top 15 products by transaction, extracted from the initial sample of 87 products.

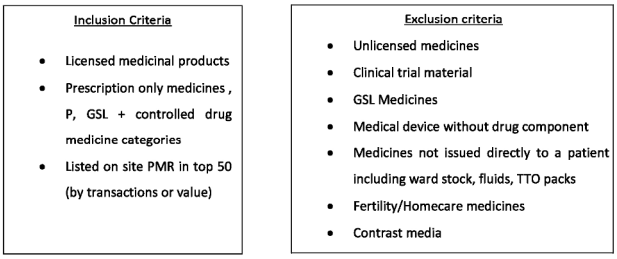


Figure 1.0: Inclusion and exclusion criteria for study medications.
Figure 1.0: Inclusion and excl
210x297mm (300 x 300 DPI)

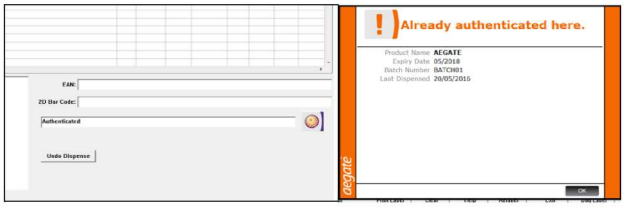


Figure 2.0: Pop-up messages triggered upon authentication of medicines that are safe for administration.
Figure 2.0: Pop-up messages tr
210x297mm (300 x 300 DPI)

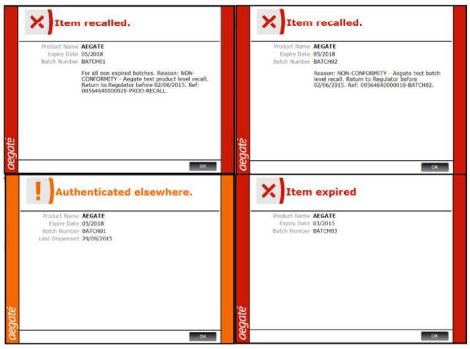


Figure 3.0: Pop-up messages triggered upon authentication of medicines requiring quarantine.
Figure 3.0: Pop-up messages tr
210x297mm (300 x 300 DPI)

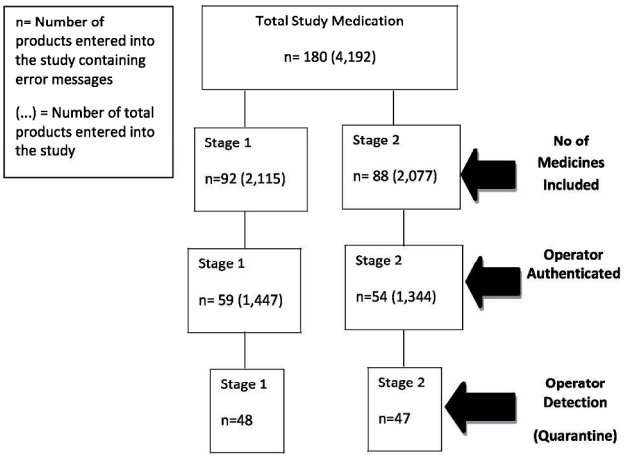
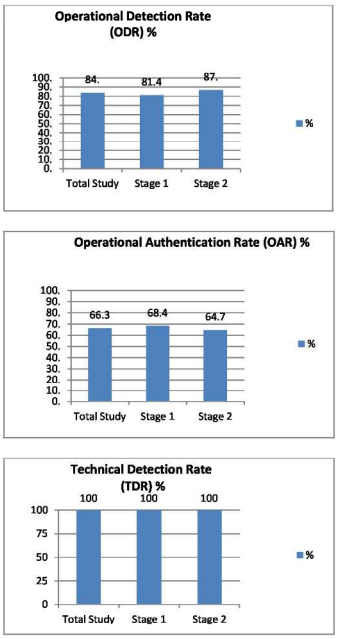


Figure 4.0 : Data tree which identified the total number of medicines serialised for each stage of the study (no. of medicines included), medicines detected by the authentication technology, stored on the secure database (operator authenticated) and finally, the total number of medicines in each stage quarantined for researcher investigation (operator detection).

Figure 4.0 : Data tree which i
210x297mm (300 x 300 DPI)



	OAR %	TDR %	ODR%
Total Study	66.3	100	84
Stage 1	68.4	100	81.4
Stage 2	64.7	100	87

Figure 5.0: Graphic and numerical representation of OAR, TDR and ODR percentages.
Figure 5.0: Graphic and numeri
210x297mm (300 x 300 DPI)

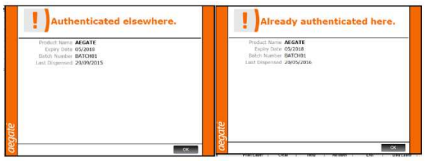


Figure 6.0: Pop up message warnings which are generated when a counterfeit medicine (Left) and a medicine which has already been authenticated on site (right) are scanned.

Figure 6.0: Pop up message war
210x297mm (300 x 300 DPI)

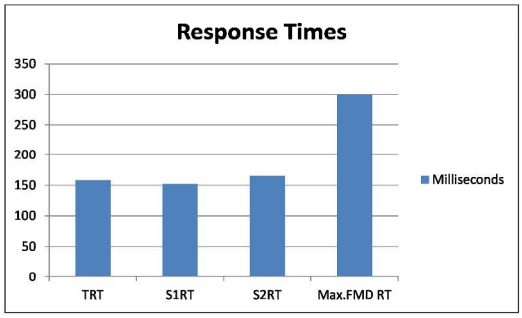


Figure 7.0: Total response times for each stage.
Figure 7.0: Total response tim
210x297mm (300 x 300 DPI)

Appendix 1.0: Total portfolio of medicines included in study.

Value	Transaction
Afatanib 40mg injection	Paracetamol 500mg tablets
Aflibercept injection	Codeine 30mg tablets
Bosutinib 500mg injection	Omeprazole 20mg capsules
Botulinum toxin type A injection	Prednisolone 5mg tablets
Darbopoetin alpha 300mcg injection	Co-amoxiclav 625mg tablets
Dexamethasone 2mg tabs	Macrogol sachets
Ferric Carboxymaltose injection	Lactulose 300ml liquid
Infliximab 100mg infusion	Dalteparin 5000 units syringe
Lenolidamide 10mg tablets	Aspirin 75mg tablets
Lenolidamide 25mg tablets	Ibuprofen 400mg tablets
Linezolid 600mg tablets	Pipperacillin/Tazobactam 4.5g injection
Pomalidamide tablets	Adcal d3 tablets
Rivaraxiban 15mg tablets	Salbutamol inhaler 100mcg
Traztuzumab 600mg injection	Morphine Sulphate 10mg/5ml solution
Pentosan polysulphate 100mg capsules	Tramadol 50mg capsules

Table 1.0: A list of the top 15 products by value and top 15 products by transaction, extracted from the initial sample of 87 products.