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Substandard and Falsified Medicine Detection in the Hospital Setting: False quarantine, offline incidents and response times

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Key Words: Health Information Technology, Offline, Falsified Medicine, Substandard Medicine, Medicine Detection, Medicine Authentication.

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Author Contributions: BN was the Principal Investigator (PI) on this study, BN collected data, BN analysed the data and BN wrote the manuscript.

Data statement: Please contact the corresponding author for access to original data.

Abstract

Objectives: To repeat the Naughton et al., 2016 method to assess the technical effectiveness of digital medicine authentication technology in a hospital setting under European Union Falsified Medicines Directive (EU FMD) conditions.

Design: 2,188 medicines were serialised using 2D data matrix labels and introduced into an operational National Health Service (NHS) hospital dispensary. Staff were asked to check medicines for 2D data matrixes and scan those products in addition to their usual medicine preparation and checking processes. Upon scanning 4% of the medicines labelled with a 2D barcode generated a pop-up which identified the medicine as either authenticated elsewhere (falsified), authenticated here, expired or recalled.

Setting: An NHS teaching hospital based in the United Kingdom and the same site as the Naughton et al., 2016 study.

Participants: General Pharmaceutical Council registered accredited accuracy checking technicians and pharmacists

Primary Outcome Measures: Response times, offline issues, false quarantine episodes and workarounds. The EU FMD maximum response time limit is 300 ms.

Results: During the checking stage of medicine preparation, the average response times for medicine authentication in this study was 131 milliseconds (ms). However, 4.67% of attempted authentications experienced offline issues, an increase of 4.23% from the previous study. An increase in offline instances existed alongside an increase in false quarantine.

Conclusions: Digital drug screening has the capability of operating with response times less than the FMD mandated limit of 300 ms. However, there was a raised incidence of offline errors and cases of false quarantine. The practical and legal implications of supplying an SF medicine during offline

periods without prior authentication, or withholding supply until online status resumes, are not yet fully understood.

Funding statement

This study was funded by Keele University and Aegate limited.

Competing interests

The author has no financial interest related to this study to disclose. The content outlined herein represents the individual opinions of the author(s) and may not necessarily represent the viewpoints of their employers. Dr Naughton is a consultant for Solfen Healthcare Limited and conducts consultancy which aims to generate impact from research.

Article Summary

Strengths and limitations of this study.

- This study is the first of its kind to assess medicines authentication response times, false quarantine and offline incidents.
- This study demonstrates the effect that offline issues can have on practice.
- This study could be improved by being performed at multiple sites.

Introduction

There are many definitions of falsified medicines internationally [1–3]. However, the World Health Organisation (WHO) defines falsified medicines as "Medical products that deliberately or fraudulently misrepresent their identity, composition or source". The WHO defines substandard medicines as "Authorized medical products that fail to meet either their quality standards or specifications or both". Substandard medicines, for example, may be medicines which originated from a legitimate manufacturer but contain an unintentional "out of specification" error in their production [4].

Examples of SF medicines are usually seen in Low and Middle-Income Countries (LMIC's), and their administration can lead to side-effects, poor treatment outcomes and death [5–8]. However, falsified medicines are not just an issue in LMIC's. There have also been examples of falsified medicines in High-Income Countries (HICs), for example, a falsified version of an anticancer agent Avastin was discovered which contained no active ingredient [9]. Moreover, there were 11 episodes of falsified medicines identified in the UK between 2001 and 2011 and 222 cases of substandard medicines recalled in the UK during the same period [10]; thus supporting the argument that SF medicines affect both LMIC's and HIC's.

There are many emerging international regulations pertaining to the identification of SF medicine. The United States (US) Drug Supply Chain Security Act [1] and the EU Falsified Medicines Directive (EUFMD) [3,11] are the most widely known regulations internationally. The DSCSA relies on a track and trace process where medicines are scanned upon transfer of

ownership while the falsified medicines directive has mandated medicine commission at production and digital drug screening or medicines authentication (MA) at the point of supply to the patient, i.e. an end to end approach. Both regulations aim to identify substandard (recalled and expired) and falsified or counterfeit medicines.

The EU FMD is a pan-European regulation which mandates medicine authentication also known as medicine decommissioning at the point of supply to the patient and involves the scanning of a two-dimensional barcode. Manufacturers are currently preparing for complete prescription only medicine (POM) serialisation. Therefore different manufacturers are at different stages of preparedness. Manufacturers must have all their new products serialised, and dispensers must have operations in place to authenticate (scan) the 2D barcode on each medicine pack dispensed from February 9th 2019 [12]. The data contained within this 2D data matrix is then digitally crosschecked against a national database to determine whether or not a medicine is recalled, expired or potentially falsified. The FMD mandated MA approach is an entirely new process for much of Europe and will affect every pharmacy throughout the EU. Each European hospital or community pharmacy must be compliant by February 9th 2019. Although this regulation has been in existence since 2011, there are low levels of awareness and understanding amongst practitioners. A publication by Naughton et al. in 2016 [13] identified issues regarding the relatively poor operational authentication and detection rate of this approach. Naughton et al., 2016 identified accuracy checking technicians and pharmacists at the checking stage of medicine supply as the best-placed personnel within the dispensary to carry out the decommissioning

process, based on scanning compliance data. The authentication technology in the Naughton et al. study did not report offline episodes or false quarantine but did report an average response time of less than 300 ms. However, not all medicines in the Naughton et al. 2016 study were scanned and of those scanned not all were appropriately quarantined in accordance with the study protocol. These results demonstrated a significant operational quality concern with the digital MA approach [13].

A repeat of the Naughton et al. study was undertaken under near-identical conditions with one alteration to the MA technology. This change involved the inclusion of an audio alert, which was suggested by study participants as part of a Delphi method study [14]. This audio alert sounded upon the authentication of a falsified medicine (authenticated elsewhere) or a substandard medicine (expired or recalled). This study generated a wealth of data relating to the incoming digital drug screening approach. The objective of this paper is to assess the technical data gathered in this study. This paper focusses on some of the key FMD parameters, i.e. offline issues, false quarantine and response times and observes the workarounds associated with the new process. The implications of the EU FMD have the potential to be hugely disruptive to healthcare delivery in the face of poor implementation. This paper aims to help healthcare providers to understand the potential technical disruption which may affect medicine supply and patient outcomes.

Methods

A follow-up study to Naughton et al., 2016 [13] was conducted to gain further understanding of the FMD process from a technical perspective and to identify

the impact of an audio alert at the point of product authentication. This study included multiple objectives, four of which are explored in this paper.

Objectives

- To establish MA technology offline frequency (i.e. how often the system failed to connect to the medicines verification database),
- To identify the frequency of false quarantine in this approach,
- To identify MA response times (i.e. how long it took for the technology to communicate with the database and return a response),
- To observe workarounds associated with the MA approach.

Study Site

This study was performed in the same NHS hospital site that hosted the baseline study by Naughton et al. in 2016, namely Oxford University Hospitals NHS Foundation Trust.

Product Serialisation Method

Medicine product lines were labelled with a pre-programmed two-dimensional barcode sticker (30 product lines in total), twice a week, in the morning and early afternoon for an eight-week period to ensure that medicine lines in the study remained serialised for the duration of the eight-week study, as per the Naughton et al., study in 2016. 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 1.0.**

Table 1.0: 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 (n=2,188)
Authenticated (Purple symbol requiring no action)	96%
Already Authenticated here (Amber)	Naturally occurring[1]
Authenticated Elsewhere/Falsified (Amber)	1%
Product Recalled (Red)	1%
Pack Recalled (Red)	1%
Pack Expired (Red)	1%

Medicines with serialised stickers attached were recorded in a database maintained by the PI; these medicine packs were then compared to the medicines quarantined by NHS staff members and those recorded as scanned by the MA provider's database. Not all medicines within the dispensary were serialised to simulate initial FMD decommissioning in a live environment, i.e. medicines manufactured before 2019 will be permitted to be sold without FMD safety features. However, any medicines manufactured beyond February 9th, 2019 will require safety features, resulting in a mix of serialised and non-serialised medicines in the supply chain.

Comparability of Studies

The method used in this study were almost identical to the approach taken in stage one of the Naughton et al. 2016 study (i.e. that medicine decommissioning was performed by pharmacists and accuracy checking technicians at the checking stage). The exception was that the technology including an audio alert which alarmed upon the attempted authentication of a medicine requiring quarantine. The same portfolio of 30 medicine lines was used over an eight-week period, and the participants were given the same

[1] If a medicine were scanned twice, the second scan would generate a pop up which stated that the medicine was 'Already Authenticated Here'. Therefore, these alerts were 'Naturally Occurring' and not introduced by the PI.

presentation and demonstration of the authentication technology as per the protocol, however, despite the best efforts of the PI, there may have been some perceived differences between both studies and these are noted in **Table 2.**

Table 2: Potential differences between Naughton et al. 2016 and the repeat study.

Naughton et al. 2016 (Stage one)	Repeat Study	Considerations
No previous exposure to MA technology	Previous exposure to MA technology	Previous results have not identified an association between technology exposure and increased compliance. There was a greater than a one-year interval between studies
Conducted as a service evaluation study	Conducted as a research study	The repeat study involved ethical approval and written consent
This study was proposed by the Principal Investigator (PI)	The study was based on a consensus improvement (audio alarm) suggested by the participants	Compliance may have been increased by the motivation to implement an idea that was suggested by the participants

Ethical Approvals

This study was classified as research according to NIHR guideline's; Keele University provided ethical approvals. Health Research Authority approvals and Trust R&D approvals were required and provided by both organisations.

Patient and Public Involvement

Patients and the public were not involved in study design or data collection as the research question regarded health information technology within a hospital setting. In this context it had little impact on patients. In a

community setting this technology may have impacted the public to a greater extent and would therefore be warranted.

Results

Naughton et al., 2016 [13] and the repeat study 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 in **Figure 1.0**.

Figure 1.0: [13].

In Naughton et al. 2016, 2,115 serialised medicines were introduced into an active, operational hospital dispensary 92 of which generated a pop-up requiring medicine quarantine; the repeat study involved a total of 2,188 medicines and of these 89 generated a pop-up identifying the medicine as requiring quarantine. According to protocol participants would then place these products in a quarantine box, away from medicines in circulation within the dispensary.

The EU FMD has mandated a maximum data round-trip (from scanning to external database and back) response rate of less than 300 ms. Across both studies, this has been achieved with a quicker response rate observed in the repeat study. Offline issues, appear to have been more frequent in the repeat study with a 4.23% increase when compared to the Naughton et al. 2016 study. False quarantines were recorded in both studies. A false quarantine refers to when a staff member incorrectly quarantines a medicine. There were 11 cases in 2015 and 37 cases in 2016. The response times and frequency of

offline issues recorded in Naughton et al., 2016 and the repeat study are outlined in **Table 3** below.

Table 3: The response times and frequency of offline issues recorded in Naughton et al. 2016 and the repeat study.

Parameter	Naughton et al., 2016	Repeat 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
*These numbers represent total scans in each study which include decommissions, verifications, duplicate scans and re-commissioning.			

The false quarantine figure for the Naughton et al. 2016 study was extracted from previously gathered unpublished data [13].

False Quarantine and False Negatives

The basis of an effective diagnostic test relies on its sensitivity and specificity. Sensitivity or true positive rate measures the proportion of positives identified as such by the test [15–17]. Specificity or true negatives, report the proportion of negatives that are correctly identified by the test [15–17]. The company providing the solution tested this technology and the PI also performed ad-hoc testing throughout the studies to ensure that medicines with pre-programmed alerts were being delivered to the staff and therefore the technical sensitivity and specificity was accepted as 1.0, granted the technology remained online. This approach is not entirely technical and relies on the interpretation of alerts from the user in a busy environment and the patience of staff to deal with offline issues. **Table 4** identified that the number of false quarantine incidents in the Naughton et al. 2016 study was 11 (of which three occurred during an

offline period). However, there were 37 cases of false quarantine in the repeat study (of which 17 were related to an offline issue). **Table 4.**

Table 4: False quarantine

	Naughton et al., 2016	Repeat Study
False Quarantine	11 (of which three were related to an offline issue)	37 (of which 17 were related to an offline issue)

Workarounds

It was observed during this study that the staff created workarounds. In instances where medicines would not scan, due to an offline issue or otherwise, staff tended to quarantine the product. This workaround demonstrates that the staff erred on the side of caution when faced with offline incidents. It was also observed that after the staff had authenticated a product that was opened and partially used they would use a pen to place across 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. This study safely assessed the response time, false quarantine frequency and offline frequency in a controlled, operating, closed-loop environment without compromising patient safety and is therefore uniquely positioned. MA has been researched in part, in studies in Belgium where the authentication of medicines has been commonplace [18]. However, there is little evidence which identifies the technical performance of the approach beyond this study.

Response Times

Throughout the Naughton et al. 2016 study and the present repeat study response times of 152 ms and 131ms were observed, respectively. The FMD limit is 300ms. Therefore, both studies are considered within the FMD response time limit.

Workarounds

Work by Debono et al., [19] explains that workarounds were employed to deliver service promptly, and also explained that localised workarounds affect other microsystems [19]. It is important to be aware of and report workarounds. Reporting ensures that 'What is happening', and 'What should be happening' is understood when making operational decisions which affect microsystems. Awareness of positive workarounds facilitates their incorporation into local policy, and SOPS's, awareness of negative workarounds allows for their outright and official discouragement. If a culture of reporting workarounds exists within a workplace, workarounds can be acknowledged, and decisions regarding related microsystems and related processes can be made, based on a complete understanding of what is happening in practice.

Bypassing health information systems is common practice in the medical context generally [20] and will become more prevalent as temporary solutions are sought for new and emerging problems with the implementation of novel medicine scanning systems. Kobyashi et al. explains that "Workarounds are a

common technique for dealing with the inherent uncertainty of dynamic work environments" [21]

. The introduction of MA technology in the hospital pharmacy environment brings about a level of inherent uncertainty, and in this study, the uncertainty has demonstrated a specific workaround which involves the crossing through of a 2D barcode rendering it unreadable. According to FMD regulation, a medicine pack requires decommissioning only once, and subsequent supplies from the same pack do not require further verification which makes this workaround a useful approach. However, the destruction of the 2D data matrix removes the opportunity for the hospital to scan that barcode for other practices such as stock taking or medicine verification at the bedside. Hospitals may wish to consider what extra value, beyond FMD compliance, they aim to achieve from serialised medicine packs before allowing or prohibiting a policy of striking through a 2D data matrix.

False Quarantine and Offline Incidents

This paper identifies an increase in false quarantine incidents between Naughton et al., 2016 and the repeat study **(Table 3)**. The MA was tested before use in each study and ad hoc testing was also performed by the PI, which aimed to identify instances of false negatives and ensure that medicines with pre-programmed alerts were being identified to the staff as such. False negatives were not identified during the testing period. However, there may have been cases where the technology gave no result, e.g. during offline periods. The number of incidences of false quarantine was compared with offline incidents. It is anticipated that the increase in offline issues resulted in

multiple attempts to scan the same medicine which contributed to a higher number of scans in the repeat study **(Table 4).** Staff observations and feedback identified that offline issues resulted in confusion. This confusion is likely to have resulted in the inappropriate quarantine of products (n=37, of which 17 were directly related to an offline issue). The effect of offline instances (when the scan from the terminal cannot communicate with the national database) on healthcare institutions may cause a delay in the supply of medicines to patients. This study suggests that an increase in offline issues will increase false quarantine and confusion if adequate support and clear alerts are not provided. An option permitted by the FMD during the offline scenario is to supply a medicine and manually enter the product details to evaluate the provenance of the product when online status resumes or halting medicine supply until the system is again online. Offline issues have a legal and practical impact. Supply without authentication from a professional litigation perspective is not yet apparent; it is currently unclear what would happen in the instance where the technology is offline, resulting in the supply of an SF medicine. Considering there were 222 cases of substandard recalled medicines and 11 cases of falsified medicine in the UK between 2001 and 2011 this scenario is likely to occur sooner rather than later [10]. From a practical perspective, the offline issues seen in this study may result in the cessation of medicine dispensing until online medicine authentication processes resume; for fear of dispensing an SF medicine. This may cause a delay in medicine supply and a backlog of dispensing in pharmacy departments. Pharmacy organisations are suggested to write Standard Operating Procedures (SOP's) which cover their stance on the supply of medicines during offline periods.

Supply without decommissioning could result in a patient receiving an SF medicine, and withholding supply could delay patient treatment or hospital dischargetal.

This study was carried out using a technology provider that had been operating in Greece, Italy and Belgium for approximately ten years. At the time, the offline issues experienced in this study were reported as having affected European clients also. This company is no longer in existence, and national databases will be provided by other companies with less experience in this niche area. There is concern that this level of offline disruption may be repeated and cause the same disruption seen in this study but on a national scale.

Conclusions and Recommendations

Response times below 300 ms are realistic and achievable under FMD conditions [13]. Therefore, average response times should not undermine MA compliance. However, offline issues may be linked to false quarantine and are likely to have caused significant delays and confusion during offline periods in the present study. Hospitals and pharmacies are suggested to review their dispensing SOP's to include guidance regarding medicine dispensing during offline periods. Hospitals and community pharmacies could also record offline periods as a risk on their risk registers. However, they could also mandate that their technology providers build in explicitly clear alerts that describe precisely what is required during offline periods and match these alerts with clear internal guidance, Standard Operating Procedures (SOP's) and training. Although this technological approach has proven its ability to operate at average speeds well below the FMD mandated limit of 300 milliseconds, it is

suggested from this study that offline issues may have an effect on false quarantine and that offline issues are likely to disrupt the delivery of medicines to patients. One way to reduce offline issues would be to penalise the National Medicines Verification System (NMVS) provider for offline instances beyond an agreed contracted level, e.g. 1%. With appropriate incentives, NMVS providers may be more likely to prioritise and rectify offline incidents.

It is important to be aware of the value of medicine serialisation and decide if an organisation wishes to grasp additional value or settle for the minimum level of legal compliance. It is suggested that the General Pharmaceutical Council (GPhC) should also provide clear guidance on the sanctions associated with failure to decommission a medicine according to EU FMD legislation.

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Figure 1.0: A diagram identifying the total number of medicines included in both studies [13].

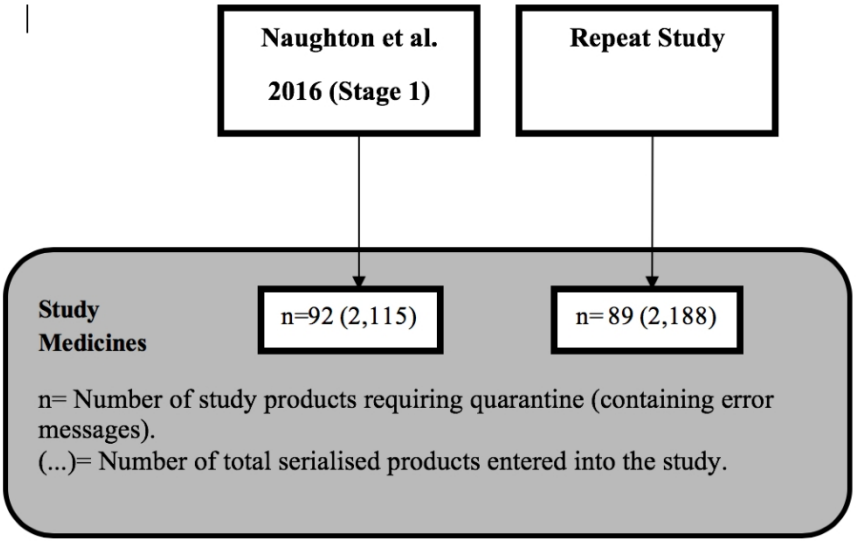

Figure 1.0: A diagram identifying the total number of medicines included in both studies [13].

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Medicine Authentication Technology in Practice: A quantitative study to assess incorrect quarantine, average response times and offline issues in the hospital setting.

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Author Contributions: BN was the Principal Investigator (PI) on this study, BN collected data, BN analysed the data and BN wrote the manuscript.

Data statement: Please contact the corresponding author for access to original data.

Abstract

Objectives: To introduce serialised medicines into an active hospital dispensary and assess the technical effectiveness of digital medicine authentication technology under European Union Falsified Medicines Directive (EU FMD) conditions.

Design: Thirty medicine lines were serialised using 2D data matrix labels and introduced into an operational UK National Health Service (NHS) hospital dispensary. Staff were asked to check medicines for 2D data matrixes and scan those products in addition to their usual medicine preparation and checking processes. Four percent of the study medicines were labelled with a 2D barcode which generated a pop-up identifying the medicine as either authenticated elsewhere (falsified), authenticated here, expired or recalled.

Setting: An NHS teaching hospital based in the United Kingdom and the same site as the Naughton et al., 2016 study.

Participants: General Pharmaceutical Council registered accredited accuracy checking technicians and pharmacists

Primary Outcome Measures: Average response times, offline issues, instances of incorrect quarantine and workarounds. The EU FMD maximum response time is 300 milliseconds.

Results: During the checking stage of medicine preparation, the average response time for medicine authentication in this study was 131 milliseconds (ms). However, 4.67% of attempted authentications experienced offline issues, an increase of 4.23% from the previous study. An increase in offline instances existed alongside an increase in incorrect quarantine.

Conclusions: Digital drug screening has the capability of operating with average response times which are below the maximum FMD limit of 300 ms. However, there was an increased incidence of offline errors and cases of incorrect quarantine. The practical and legal implications of supplying an

Substandard or Falsified medicine during offline periods without prior authentication, or withholding supply until online status resumes, are not yet fully understood.

Funding statement

This study was funded by Keele University.

Competing interests

The author has no financial interest related to this study to disclose. The content outlined herein represents the individual opinions of the author(s) and may not necessarily represent the viewpoints of their employers. Dr Naughton is a consultant for Solfen Healthcare Limited and conducts consultancy which aims to generate impact from research.

Article Summary

Strengths and limitations of this study.

- This study methodology is the first of its kind to assess medicines authentication average response times, incorrect quarantine and offline incidents within an active healthcare context.
- This study provides evidence of offline issues and demonstrates the effect that these instances can have on practice.
- This study identifies the strengths and limitations of medicines authentication technology.
- This study could be improved by being performed and compared to multiple UK sites.
- This study could be improved by being repeated in multiple EU countries.

Introduction

There definition of a falsified medicine differs internationally [1–3]. However, the World Health Organisation (WHO) defines falsified medicines as "Medical products that deliberately or fraudulently misrepresent their identity, composition or source". The WHO defines substandard medicines as "Authorized medical products that fail to meet either their quality standards or specifications or both". Substandard medicines, for example, may be medicines which originated from a legitimate manufacturer but contain an unintentional "out of specification" error in their production [4].

Instances of Substandard and Falsified (SF) medicines are usually seen in Low and Middle-Income Countries (LMIC's), and their administration can lead to side-effects, poor treatment outcomes and death in already life-threatening conditions such as malaria [5–8]. However, falsified medicines are not just an issue in LMIC's. There have also been examples of falsified medicines in High-Income Countries (HICs), for example, a falsified version of an anticancer agent Avastin was discovered which contained no active ingredient [9]. Moreover, there were 11 episodes of falsified medicines identified in the UK between 2001 and 2011 and 222 cases of substandard medicines recalled in the UK during the same period [10]; thus supporting the argument that SF medicines affect both LMIC's and HIC's.

There are many emerging international regulations pertaining to the identification of SF medicine. The United States (US) Drug Supply Chain Security Act (DSCSA) [1] and the EU Falsified Medicines Directive (EUFMD) [3,11] are the most widely known regulations internationally. The DSCSA relies

on a track and trace process where medicines are scanned upon transfer of ownership while the falsified medicines directive has mandated medicine commission at production and digital drug screening or medicines authentication (MA) at the point of supply to the patient, i.e. an end to end operation. Both regulations aim to identify substandard (recalled and expired) and falsified or counterfeit medicines.

The EU FMD is a pan-European regulation which mandates medicine authentication also known as medicine decommissioning at the point of supply to the patient and involves the scanning of a two-dimensional barcode. Manufacturers are currently preparing for prescription only medicine (POM) serialisation. Therefore different manufacturers are at different stages of preparedness. Manufacturers must have all of their new products serialised, and dispensers must have operations in place to authenticate (scan) the 2D barcode on each medicine pack dispensed from February 9th 2019 [12]. The data contained within this 2D data matrix is then digitally crosschecked against a national database to determine whether or not a medicine is recalled, expired or potentially falsified. The FMD mandated MA approach is an entirely new process for much of Europe and will affect every pharmacy throughout the EU. Each European hospital or community pharmacy must be compliant by February 9th 2019. Although this regulation has been anticipated since 2011, there are low levels of awareness and understanding amongst practitioners. A publication by Naughton et al. 2016 [13] identified issues regarding the relatively poor operational authentication and detection rate of this approach. Naughton et al., 2016 identified accuracy checking technicians and pharmacists at the checking stage of medicine supply as the best-placed personnel within

dispensary operations to carry out the decommissioning process, based on scanning compliance data. The authentication technology in the Naughton et al. study did not report offline episodes or incorrect quarantine but did report an average response time of less than 300 ms. These results demonstrated a significant operational quality concern with the digital MA approach [13]. The implications of the EU FMD have the potential to be hugely disruptive to healthcare delivery in the face of poor implementation. This paper aims to help healthcare providers to understand the potential technical disruption which may affect medicine supply and patient outcomes.

Methods

The data from the Naughton et al. 2016 study was re-examined to identify the incidence of offline errors, and incorrect quarantine. The Naughton et al. 2016 study methodology was then repeated under near-identical conditions with one alteration to the MA technology. This change involved the inclusion of an audio alert, which was suggested by study participants as part of a Delphi method study [14]. This audio alert sounded upon the authentication of a falsified medicine (authenticated elsewhere) or a substandard medicine (expired or recalled). This study generated a large data set relating to the incoming digital drug screening approach. The objective of this paper is to assess the technical data gathered in this study and compare it with previously published and unpublished data from the Naughton et al study in 2016. This paper focusses on some of the key FMD parameters, i.e. offline issues, incorrect quarantine and average response times and observes the workarounds associated with the proposed medicine authentication operation. Although the wider study included

multiple objectives, only the four technical objectives below, are explored in this paper.

Objectives

- To establish MA technology offline frequency from the Naughton et al. 2016 study (i.e. how often the system failed to connect to the medicines verification database) and to repeat the study for comparative purposes,
- To identify the frequency of incorrect quarantine in the Naughton et al. 2016 study and to repeat the study for comparative purposes,
- To identify MA average response times in the repeat study (i.e. how long it took for the technology to communicate with the database and return a response) and to compare this to the published results in Naughton et al., 2016,
- To report and discuss workarounds observed with the MA approach in the Naughton et al. 2016 study and the repeat study.

Study Site

This study was performed at the same NHS hospital site that hosted the baseline study by Naughton et al. in 2016, namely Oxford University Hospitals NHS Foundation Trust.

Product Serialisation Method

Medicine product lines were labelled with a pre-programmed two-dimensional barcode sticker (30 product lines in total), twice a week, in the morning and early afternoon for an eight-week period to ensure that medicine lines in the study remained serialised for the duration of the eight-week study, as per the Naughton et al., study in 2016. 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 1.0.**

Table 1.0: 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 (n=2,188)
Authenticated (Purple symbol requiring no action)	96%
Already Authenticated here (Amber)	Naturally occurring[1]
Authenticated Elsewhere/Falsified (Amber)	1%
Product Recalled (Red)	1%
Pack Recalled (Red)	1%
Pack Expired (Red)	1%

Medicines with serialised stickers attached were recorded in a database maintained by the PI; these medicine packs were then compared to the medicines quarantined by NHS staff members and those recorded as scanned by the MA provider's database. Not all medicines within the dispensary were serialised to simulate initial FMD decommissioning in a live environment, i.e. medicines manufactured before 2019 will be permitted to be sold without FMD safety features. However, any medicines manufactured beyond February 9th, 2019 will require safety features, resulting in a mix of serialised and non-serialised medicines in the hospital pharmaceutical supply chain.

Comparability of Studies

The methods used in this study were almost identical to the approach taken in stage one of the Naughton et al. 2016 study (i.e. that medicine decommissioning was performed by pharmacists and accuracy checking technicians at the checking stage). The exception was that the technology included an audio alert

[1] If a medicine were scanned twice, the second scan would generate a pop up which stated that the medicine was 'Already Authenticated Here'. Therefore, these alerts were 'Naturally Occurring' and not introduced by the PI.

which alarmed upon the attempted authentication of a medicine requiring quarantine. The same portfolio of 30 medicine lines 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. However, despite the best efforts of the PI, there may have been some perceived differences between both studies and these are noted in **Table 2.**

Table 2: Potential differences between Naughton et al. 2016 and the repeat study.

Naughton et al. 2016 (Stage one)	Repeat Study	Considerations
No previous exposure to MA technology	Previous exposure to MA technology	Previous results have not identified an association between technology exposure and increased compliance. There was a greater than a one-year interval between studies
Conducted as a service evaluation study	Conducted as a research study	The repeat study involved ethical approval and written consent
This study was proposed by the Principal Investigator (PI)	The study was based on a consensus improvement (audio alarm) suggested by the participants	Compliance may have been increased by the motivation to implement an idea that was suggested by the participants

Ethical Approvals

This study was classified as research according to NIHR guideline's; Keele University provided ethical approvals. Health Research Authority approvals and Trust R&D approvals were required and provided by both organisations.

Patient and Public Involvement

Patients and the public were not involved in study design or data collection as the research question regarded health information technology within a hospital setting. In this context it had little impact on patients. In a community setting this technology may have impacted the public to a greater extent and would therefore be warranted.

Results

This repeat study involved a total of 2,188 medicines and of these, 89 generated a pop-up identifying the medicine as requiring quarantine. [Figure 1.0].

Figure 1.0: [13].

The EU FMD has mandated a maximum data round-trip (from scanning to external database and back) response rate of less than 300 ms. Across both studies, this has been achieved with a quicker response time observed in the repeat study [Table 3]. Offline issues, appear to have been more frequent in the repeat study with a 4.23% increase when compared to the unpublished data collected as part of the Naughton et al. 2016 study. Incorrect quarantines were recorded in both studies. An incorrect quarantine refers to when a staff member quarantines a medicine that does not generate an alert pop-up. There were 11 cases in 2015 and 37 cases in 2016. The response times and frequency of offline issues recorded in Naughton et al., 2016 and the repeat study are outlined in **Table 3** below.

Table 3: The average response times and frequency of offline issues recorded in Naughton et al. 2016 and the repeat study.

Parameter	Naughton et al., 2016	Repeat Study	Expected Standard
MAT average response times	152 ms (n=1604*)	131ms (n=2503*)	300 ms

MAT Offline frequency	0.44% (n=1604)	4.67% (n=2503)	Undefined
*These numbers represent total scans in each study which include decommissions, verifications, duplicate scans and re-commissioning.			

The offline incidents and incorrect quarantine figures were extracted from unpublished data which was collected as part of the Naughton et al. 2016 project [13].

Incorrect Quarantine and False Negatives

The number of incorrect quarantine incidents from the Naughton et al., 2016 study and the repeat study are displayed in **Table 4.** There were 11 cases in the 2016 study (of which three occurred during an offline period). However, there were 37 cases of incorrect quarantine in the repeat study (of which 17 were related to an offline issue). **Table 4.**

Table 4: Incorrect quarantine

	Naughton et al., 2016	**Repeat Study**
Incorrect Quarantine	11 (of which three were related to an offline issue)	37 (of which 17 were related to an offline issue)

Workarounds

It was observed during this study that staff created workarounds. In instances where medicines would not scan, due to an offline issue or otherwise, staff tended to quarantine the product. This workaround demonstrates that the staff erred on the side of caution when faced with offline incidents. It was also observed that after the staff had authenticated a product that was opened and partially 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. This study safely assessed the average response time, the frequency of incorrect quarantine and offline frequency in a controlled, operating, closed-loop environment without compromising patient safety and is therefore uniquely positioned. MA has been researched in part, in studies in Belgium where the authentication of medicines has been commonplace (15). However, there is little evidence which identifies the technical performance of the approach beyond this study**.** Naughton et al., 2016 [13] and the repeat study 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 in **Figure 1.0**.

Average Response Times

Medicine dispensing within a large university hospital occurs in stages. Broadly speaking the prescription is clinically screened, it is labelled, it is dispensed and it is checked. An additional step, such as medicine authentication, could have an impact on prescription processing operation and more specifically the total prescription turn-around time. However, in this case we identify that on average communication from a terminal to a national database will not necessarily be a rate limiting step. Throughout the Naughton et al. 2016 study and the present repeat study, average response times of 152 ms and 131ms, respectively, were observed. These two studies provide evidence that the medicine authentication

operation can be performed comfortably within the EU FMD limit of 300 ms, which may reassure UK stakeholders. Although the response times in this study are positive, medicine authentication is not a micro-process which exists in isolation. Instead it should be considered as an additional step which impacts adjacent processes. Therefore, the key to success is not a sub-300 ms response time, but a well thought out re-consideration of current operations in light of this additional step.

Workarounds

Work by Debono et al., (16) explains that workarounds are employed to deliver service promptly, and also explained that localised workarounds affect other microsystems (16). It is important to be aware of and report workarounds. Reporting ensures that "What is happening", and "What should be happening" is understood when making operational decisions which affect microsystems. Awareness of positive workarounds facilitates their incorporation into local policy, and Standard Operating Procedures (SOPS's), awareness of negative workarounds allows for their outright and official discouragement. If a culture of reporting workarounds exists within a workplace, workarounds can be acknowledged, and decisions regarding microsystems and related processes can be made, based on a complete understanding of practice. Bypassing health information systems is common in the medical context (17) and will become more common as poorly designed solutions are sought for emerging problems. Kobyashi et al. explains that "Workarounds are a common technique for dealing with the inherent uncertainty of dynamic work environments" (18). The introduction of MA technology and the associated operations in the hospital

pharmacy environment brings about a level of inherent uncertainty, and in this study, this uncertainty has demonstrated a specific workaround which involves the crossing through of a 2D barcode rendering it unreadable, a new phenomenon which was observed consistently a cross both studies. According to FMD regulation, a medicine pack requires decommissioning only once, and subsequent supplies from the same pack do not require further verification which makes this workaround a useful approach. However, the destruction of the 2D data matrix removes the opportunity for the hospital to scan that barcode for other practices such as stock taking or medicine verification at the bedside. Hospitals may wish to consider what extra value, if any, beyond FMD compliance, they aim to achieve from serialised medicine packs before allowing or prohibiting a policy of striking through a 2D data matrix.

Incorrect Quarantine and Offline Incidents

The basis of an effective diagnostic test relies on its sensitivity and specificity. Sensitivity or true positive rate measures the proportion of positives identified as such by the test (19–21). Specificity or true negatives, report the proportion of negatives that are correctly identified by the test (19–21). However, this approach is not entirely technical and relies on the interpretation of alerts from the user in a busy environment and the patience of staff to deal with offline issues. The MA technology was tested before use in each study and ad hoc testing was also performed by the PI, which aimed to identify instances of false negatives and ensure that medicines with pre-programmed alerts were being identified to the staff as such. False negatives were not identified during the testing period therefore the sensitivity and specificity was deemed to be 100% when the technology was online. However, there may have been cases where

the technology gave no result, e.g. during offline periods. The number of incidences of incorrect quarantine was compared with offline incidents. It is anticipated that the increase in offline issues resulted in multiple attempts to scan the same medicine which contributed to a higher number of scans in the repeat study **(Table 3).** Staff observations and feedback identified that offline issues resulted in confusion. This confusion is likely to have resulted in a higher number of inappropriate product quarantines in the repeat study (n=37, of which 17 were directly related to an offline issue). The effect of offline instances (when the scan from the terminal cannot communicate with the national database) on healthcare institutions may cause a delay in the supply of medicines to patients. This study suggests that the increase in offline issues between both studies is responsible for the increased incorrect quarantine rate and confusion, which is likely to be problematic in the face of inadequate support and clear information technology alerts. An option permitted by the FMD during the offline scenario is to supply a medicine and manually enter the product details to evaluate the provenance of the product when online status resumes or halting medicine supply until the system is again online. Offline issues have a legal and practical impact. Supply without authentication from a professional litigation perspective is not yet apparent; it is currently unclear what would happen in the instance where the technology is offline, resulting in the supply of an SF medicine. Considering there were 222 cases of substandard recalled medicines and 11 cases of falsified medicine in the UK between 2001 and 2011 this scenario is likely to occur sooner rather than later [10]. From a practical perspective, the offline issues seen in this study may result in the cessation of medicine dispensing until online medicine authentication processes

resumes; for fear of dispensing an SF medicine. This may cause a delay in medicine supply and a backlog of dispensing in pharmacy departments. Pharmacy organisations are suggested to write Standard Operating Procedures (SOP's) which cover their stance on the supply of medicines during offline periods. Supply without decommissioning could result in a patient receiving an SF medicine, and withholding supply could delay patient treatment or hospital discharge.

This study was carried out using a technology provider that had been operating in Greece, Italy and Belgium for approximately ten years. At the time, the offline issues experienced in this study were reported as having affected European clients also. This company is no longer in existence, and national databases will be provided by other companies with less experience in this niche area. There is concern that this level of offline disruption may be repeated and cause the same disruption seen in this study, but on a national scale.

Conclusions and Recommendations

Average response times below 300 ms are realistic and achievable under FMD conditions [13]. Therefore, average response times should not undermine MA effectiveness. However, offline issues may be linked to incorrect quarantine and are likely to have caused significant delays and confusion during offline periods in the present study. Hospitals and pharmacies are suggested to review their dispensing SOP's to include guidance regarding medicine dispensing operations during offline periods. Hospitals and community pharmacies could also record offline periods as a risk on their risk registers. However, they could also mandate that their technology providers build in explicitly clear alerts that describe precisely what is required during offline periods and match these alerts

with clear internal guidance, Standard Operating Procedures (SOP's) and training. Although this technological approach has proven its ability to operate at average response times well below the FMD mandated limit of 300 milliseconds, it is suggested from this study that offline issues may have an effect on incorrect quarantine and that offline issues are likely to disrupt the delivery of medicines to patients. One way to reduce offline issues would be to penalise the National Medicines Verification System (NMVS) provider for offline instances beyond an agreed contracted level. With appropriate incentives, NMVS providers may be more likely to prioritise and rectify offline incidents.

It is important to be aware of the value of medicine serialisation and decide if an organisation wishes to grasp additional value or settle for the minimum level of legal compliance. It is suggested that the General Pharmaceutical Council (GPhC) should also provide clear guidance on the sanctions associated with failure to decommission a medicine according to EU FMD legislation.

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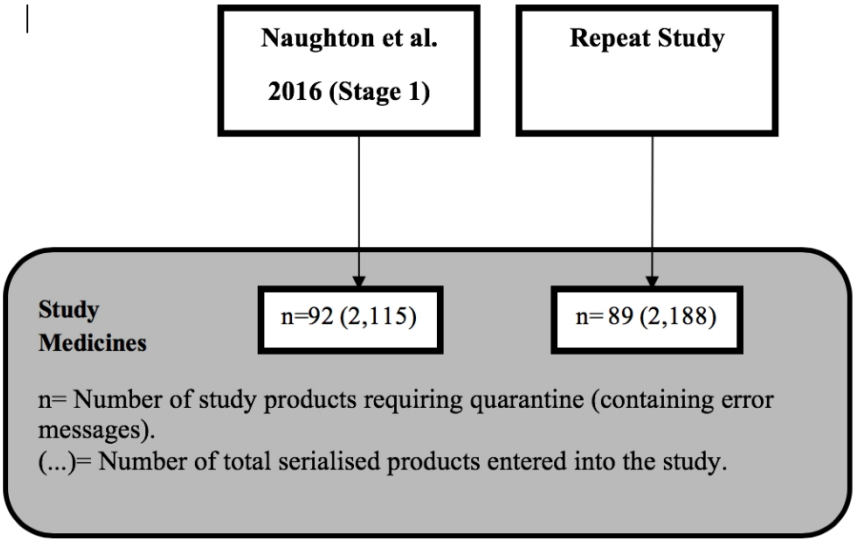

Figure 1.0: A diagram identifying the total number of medicines included in both studies [13].

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Medicine Authentication Technology: A quantitative study of incorrect quarantine, average response times and offline issues in a hospital setting

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Medicine Authentication Technology: A quantitative study of incorrect quarantine, average response times and offline issues in a hospital setting.

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Author Contributions: BN was the Principal Investigator (PI) on this study, BN collected data, BN analysed the data and BN wrote the manuscript.

Data statement: Please contact the corresponding author for access to original data.

Abstract

Objectives: To introduce serialised medicines into an active hospital dispensary and assess the technical effectiveness of digital medicine authentication technology under European Union Falsified Medicines Directive (EU FMD) conditions.

Design: Thirty medicine lines were serialised using 2D data matrix labels and introduced into an operational United Kingdom (UK) National Health Service (NHS) hospital dispensary. Staff were asked to check medicines for 2D data matrixes and scan those products in addition to their usual medicine preparation and checking processes. Four per cent of the study medicines were labelled with a 2D barcode which generated a pop-up identifying the medicine as either authenticated elsewhere (falsified), authenticated here, expired or recalled.

Setting: An NHS teaching hospital based in the United Kingdom and the same site as the Naughton et al., 2016 study.

Participants: General Pharmaceutical Council registered accredited accuracy checking technicians and pharmacists

Primary Outcome Measures: Average response times, offline issues, instances of incorrect quarantine and workarounds. The EU FMD maximum response time is 300 milliseconds.

Results: During the checking stage of medicine preparation, the average response time for medicine authentication in this study was 131 milliseconds (ms). However, 4.67% of attempted authentications experienced offline issues, an increase of 4.23% from the previous study. An increase in offline instances existed alongside an increase in incorrect quarantine.

Conclusions: Digital drug screening has the capability of operating with average response times which are below the maximum EU FMD limit of 300 ms. However, there was an increased incidence of offline errors and cases of incorrect quarantine. The practical and legal implications of supplying a

Substandard or Falsified medicine during offline periods without prior authentication, or withholding supply until online status resumes, are not yet fully understood.

Funding statement

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Competing interests

The author has no financial interest related to this study to disclose. The content outlined herein represents the individual opinions of the author(s) and may not necessarily represent the viewpoints of their employers. Dr Naughton is a consultant for Solfen Healthcare Limited and conducts consultancy which aims to generate impact from research.

Article Summary

Strengths and limitations of this study.

- This methodology is the first of its kind to assess medicine authentication average response times, incorrect quarantine and offline incidents within an active healthcare context.
- Evidence of offline issues and their effect on practice is demonstrated in this article.
- This study identifies the strengths and limitations of medicine authentication technology.
- As this study was not conducted at multiple hospitals it provides case study evidence only.
- This research assesses manual medicine authentication and does not provide evidence for automated or robotic dispensing systems.

Introduction

The definition of a falsified medicine differs internationally [1–3]. However, the World Health Organisation (WHO) defines falsified medicines as "Medical products that deliberately or fraudulently misrepresent their identity, composition or source". The WHO defines substandard medicines as "Authorized medical products that fail to meet either their quality standards or specifications or both". Substandard medicines, for example, may be medicines which originated from a legitimate manufacturer but contain an unintentional "out of specification" error in their production [4].

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Medicine serialisation regulations are emerging internationally. The United States (US) Drug Supply Chain Security Act (DSCSA) [1] and the EU Falsified Medicines Directive (EUFMD) [3,11] are the most widely known. The DSCSA relies on a track and trace process where medicines are scanned upon transfer of ownership while the falsified medicines directive has mandated medicine

commission at production and digital drug screening or medicines authentication (MA) at the point of supply to the patient, i.e. an end to end operation. Both regulations aim to identify substandard (recalled and expired) and falsified or counterfeit medicines.

The EU FMD is a pan-European regulation which mandates medicine authentication also known as medicine decommissioning at the point of supply to the patient and involves the scanning of a two-dimensional barcode. Manufacturers are currently preparing for prescription only medicine (POM) serialisation and are at different stages of preparedness. Manufacturers must serialise products which are manufactured after February 9th 2019, and dispensers must have operations in place to authenticate (scan) the 2D barcode on each medicine pack dispensed from February deadline [12]. The data contained within this 2D data matrix is then digitally crosschecked against a national database to determine whether or not a medicine is recalled, expired or potentially falsified. The FMD mandated MA approach is an entirely new process for much of Europe and will affect every pharmacy throughout the EU. Each European hospital or community pharmacy must be compliant by February 9th 2019. Although this regulation has been anticipated since 2011, there are low levels of awareness and understanding amongst practitioners and a publication by Naughton et al. 2016 [13] identified issues regarding the relatively poor operational authentication and detection rate of this approach. Naughton et al., 2016 identified accuracy checking technicians and pharmacists at the checking stage of medicine supply as the best-placed personnel within dispensary operations to carry out the decommissioning process, based on scanning compliance data. The Naughton et al. study did not discuss offline

episodes or incorrect quarantine but did report an average response time of less than 300 ms. These results demonstrated a significant operational quality concern with the digital MA approach [13]. If poorly implemented, the EU FMD has the potential to be disruptive to healthcare provision. This paper aims to inform healthcare providers regarding the potential technical disruption caused by the incoming legislation.

Methods

Data from the Naughton et al. 2016 study was re-examined to identify the incidence of offline errors, and incorrect quarantine. The Naughton et al. 2016 study methodology was then repeated under near-identical conditions with one alteration to the MA technology. This change involved the inclusion of an audio alert, which was suggested by study participants as part of a Delphi method study [14]. This audio alert sounded upon the authentication of a falsified medicine (authenticated elsewhere) or a substandard medicine (expired or recalled). This study generated a large data set relating to the incoming digital drug screening approach. The objective of this paper is to assess the technical data gathered in the wider study and compare it with previously published and unpublished data from the Naughton et al study in 2016. This paper focusses on some of the key technical FMD parameters, i.e. offline issues, incorrect quarantine and average response times and observes the workarounds associated with the proposed medicine authentication operation. Although the wider study included multiple objectives, only the three technical objectives below, are explored in this paper.

Objectives

- To establish MA technology offline frequency (i.e. how often the system failed to connect to the medicines verification database) and incorrect quarantine in the repeat study and compare it with previously unpublished data collected as part of the Naughton et al., 2016 study.
- To identify MA average response times in the repeat study (i.e. how long it took for the technology to communicate with the database and return a response) and compare this to the published results in Naughton et al., 2016,
- To observe and discuss workarounds associated with the MA approach in the repeat study and to acknowledge the effect of the audio alert on the technical parameters measured in this study.

Study Site

This study was performed at the same NHS hospital site that hosted the study by Naughton et al. in 2016, namely Oxford University Hospitals NHS Foundation Trust.

Product Serialisation Method

Medicine product lines were labelled with a pre-programmed two-dimensional barcode sticker (30 product lines in total), twice a week, in the morning and early afternoon for an eight-week period to ensure that medicine lines remained serialised throughout the duration of the eight-week study, as per the Naughton et al., study in 2016. 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 1.0.**

Table 1.0: 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 (n=2,188)
Authenticated (Purple symbol requiring no action)	96%

Already Authenticated here (Amber)	Naturally occurring[1]
Authenticated Elsewhere/Falsified (Amber)	1%
Product Recalled (Red)	1%
Pack Recalled (Red)	1%
Pack Expired (Red)	1%

Medicines with serialised stickers attached were recorded in a database maintained by the PI; these medicine packs were then compared to the medicines quarantined by NHS staff members and those recorded as scanned by the MA provider's database. Not all medicines within the dispensary were serialised to simulate initial FMD decommissioning in a live environment, i.e. an environment which contains a mix of serialised and non-serialised medicines.

Comparability of Studies

The methodology used in the repeat study were identical to those in stage one of the Naughton et al. 2016 study (medicine decommissioning performed by pharmacists and accuracy checking technicians at the checking stage). However, the technology included an audio alert which alarmed upon the attempted authentication of a medicine requiring quarantine. The same portfolio of 30 medicine lines 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 PI, there may have been some perceived differences between both studies and these are noted in **Table 2.**

[1] If a medicine were scanned twice, the second scan would generate a pop up which stated that the medicine was 'Already Authenticated Here'. Therefore, these alerts were 'Naturally Occurring' and not introduced by the PI.

Table 2: Potential differences between Naughton et al. 2016 and the repeat study.

Naughton et al. 2016 (Stage one)	Repeat Study	Considerations
No previous exposure to MA technology	Previous exposure to MA technology	Previous results have not identified an association between technology exposure and increased compliance. There was a greater than a one-year interval between studies
Conducted as a service evaluation study	Conducted as a research study	The repeat study involved ethical approval and written consent
This study was proposed by the Principal Investigator (PI)	The study was based on a consensus improvement (audio alarm) suggested by the participants	Compliance may have been affected by the motivation to implement an idea that was suggested by the participants

Ethical Approvals

This study was classified as research according to NIHR guideline's; Keele University provided ethical approvals. Health Research Authority approvals and Trust R&D approvals were required and provided by both organisations.

Patient and Public Involvement

Patients and the public were not involved in study design or data collection as the research question regarded health information technology within a hospital setting. In this context it had little impact on patients.

Results

This repeat study involved a total of 2,188 medicines and of these, 89 generated a pop-up identifying the medicine as requiring quarantine. [Figure 1.0].

Figure 1.0: [13].

The EU FMD has mandated a maximum data round-trip (from scanning to external database and back) response rate of less than 300 ms. Across both studies, this has been achieved with a quicker response time observed in the repeat study [Table 3]. Offline issues, appear to have been more frequent in the repeat study with a 4.23% increase when compared to the unpublished data collected as part of the Naughton et al. 2016 study. Incorrect quarantine was recorded in both studies. An incorrect quarantine refers to when a staff member quarantines a medicine that does not generate an alert pop-up. There were 11 cases in 2015 and 37 cases in 2016. The response times and frequency of offline issues recorded in Naughton et al., 2016 and the repeat study are outlined in **Table 3** below.

Table 3: The average response times and frequency of offline issues recorded in Naughton et al. 2016 and the repeat study.

Parameter	Naughton et al., 2016	Repeat Study	Expected Standard
MAT average response times	152 ms (n=1604*)	131ms (n=2503*)	300 ms
MAT Offline frequency	0.44% (n=1604)	4.67% (n=2503)	Undefined
*These numbers represent total scans in each study which include decommissions, verifications, duplicate scans and re-commissioning.			

The offline incidents and incorrect quarantine figures were extracted from unpublished data which was collected as part of the Naughton et al. 2016 study [13].

Incorrect Quarantine

The number of incorrect quarantine incidents from the Naughton et al., 2016 study and the repeat study are displayed in **Table 4.** There were 11 cases in the

2016 study (of which three occurred during an offline period). However, there were 37 cases of incorrect quarantine in the repeat study (of which 17 were related to an offline issue). **Table 4.**

Table 4: Incorrect quarantine

	Naughton et al., 2016	Repeat Study
Incorrect Quarantine	11 (of which three were related to an offline issue)	37 (of which 17 were related to an offline issue)

Workarounds

It was observed during this study that staff created workarounds. In instances where medicines would not scan, due to an offline issue or otherwise, staff tended to quarantine the product. This workaround demonstrates that the staff erred on the side of caution when faced with offline incidents. It was also observed that after the staff had authenticated a product that was opened and partially used they would use a pen to place a cross through the 2D data matrix to identify the part pack medicine as 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. This study safely assessed the average response time, the frequency of incorrect quarantine and offline frequency in a controlled, operating, closed-loop environment without compromising patient safety and is therefore uniquely positioned. Although the addition of the audio alert did not appear to affect the technical parameters measured in this paper i.e. technology response times, false quarantine or offline instances. Further, research is

required to understand the effect of this user instigated alteration on overall technology use and compliance.

MA has been researched in part, in studies in Belgium where the authentication of medicines has been commonplace [15]. However, there is little evidence which identifies the technical performance of the approach beyond this study**.** Naughton et al., 2016 [13] and the repeat study 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 in **Figure 1.0**.

Average Response Times

Medicine dispensing within a large university hospital occurs in stages. Broadly speaking the prescription is clinically screened, labelled, dispensed and checked. An additional step, such as medicine authentication, could have an impact on prescription processing operations and more specifically the prescription turn-around time. However, in this case we identify that on average communication from a terminal to a national database will not necessarily be a rate limiting step. Throughout the Naughton et al. 2016 study and the present repeat study, average response times of 152 ms and 131ms, respectively, were observed. These two studies provide evidence that the medicine authentication operation can be performed comfortably within the EU FMD limit of 300 ms, which may reassure UK stakeholders. Although the response times in this study are positive, medicine authentication is not a micro-process which exists in isolation. Instead it should be considered as an additional step which impacts adjacent processes. Therefore, the key to success is not a sub-300 ms response

time, but a well thought out re-consideration of current operations in light of this additional step.

Workarounds

Work by Debono et al., (16) explains that workarounds are employed to deliver service promptly, and also explained that localised workarounds affect other microsystems (16). It is important to be aware of and to report workarounds. Reporting ensures that "What is happening", and "What should be happening" is understood when making operational decisions which affect microsystems. Awareness of workarounds generating positive outcomes, facilitates their incorporation into local policy, and Standard Operating Procedures (SOPs) while awareness of workarounds with negative outcomes facilitates their documentation and management . If a culture of reporting workarounds exists within a workplace, workarounds can be acknowledged, and decisions regarding microsystems and related processes can be made, based on a complete understanding of practice.

Bypassing health information systems is common in the medical context [17] and may become more common if digital healthcare systems are not responsibly designed. Kobyashi et al. explains that "Workarounds are a common technique for dealing with the inherent uncertainty of dynamic work environments" [18]. The introduction of MA technology and the associated operations in the hospital pharmacy environment brings about this level of inherent uncertainty, and in this study, this uncertainty has demonstrated a specific workaround which involves the crossing through of a 2D barcode

rendering it unreadable, a new phenomenon which was observed consistently across the study. According to FMD regulation, a medicine pack requires decommissioning only once, and subsequent supplies from the same pack do not require further verification which makes this workaround a useful approach. However, the destruction of the 2D data matrix removes the opportunity for the hospital to scan that barcode for other practices such as stock taking or medicine verification at the bedside. Hospitals may wish to consider what extra value, if any, beyond FMD compliance, they aim to achieve from serialised medicine packs before allowing or prohibiting a policy of striking through a 2D data matrix.

Incorrect Quarantine and Offline Incidents

The basis of an effective diagnostic test relies on its sensitivity and specificity. Sensitivity or true positive rate measures the proportion of positives identified as such by the test [19–21]. Specificity or true negatives, report the proportion of negatives that are correctly identified by the test [19–21]. However, this approach is not entirely technical and relies on the interpretation of alerts from the user in a busy environment and the patience of staff to deal with offline issues. The MA technology was tested before use in each study and ad hoc testing was also performed by the PI, which aimed to identify instances of false negatives and ensure that medicines with pre-programmed alerts were being identified to the staff as such. False negatives were not identified during the testing period therefore the sensitivity and specificity was deemed to be 100% when the technology was online. However, there may have been cases where the technology gave no result, e.g. during offline periods. The number of incidences of incorrect quarantine was compared with offline incidents and it is

anticipated that the increase in offline issues resulted in multiple attempts to scan the same medicine which contributed to a higher number of scans in the repeat study **(Table 3).** Staff observations and feedback identified that offline issues resulted in confusion, leading to a higher number of inappropriate product quarantines in the repeat study (n=37, of which 17 were directly related to an offline issue). The effect of offline instances (when the scan from the terminal cannot communicate with the national database) on healthcare institutions may therefore, cause a delay in the supply of medicines to patients. This study suggests that the increase in offline issues is responsible for the increased incorrect quarantine rate and confusion at the point of decommissioning; which is likely to be augmented by inadequately designed information technology alerts. An option permitted by the FMD during the offline scenario is to supply a medicine and manually enter the product details to evaluate the provenance of the product when online status resumes or halting medicine supply until the system is again online. Offline issues have a legal and practical impact. Supply without authentication from a professional litigation perspective is not yet apparent; it is currently unclear what would happen in the instance where the technology is offline, resulting in the supply of an SF medicine. Considering there were 222 cases of substandard recalled medicines and 11 cases of falsified medicine in the UK between 2001 and 2011 this scenario is likely to occur sooner rather than later [10]. From a practical perspective, the offline issues seen in this study may result in the cessation of medicine dispensing until online medicine authentication processes resumes; for fear of dispensing an SF medicine. This may cause a delay in medicine supply and a backlog of dispensing in pharmacy departments. Pharmacy organisations are suggested to

write Standard Operating Procedures (SOPs) which cover their stance on the supply of medicines during offline periods. Supply without decommissioning could result in a patient receiving an SF medicine, and withholding supply could delay patient treatment or hospital discharge.

This study was carried out using a technology provider that had been operating in Greece, Italy and Belgium for approximately ten years. At the time, the offline issues experienced in this study were reported as having affected European clients also. This company is no longer in existence, and national databases will be provided by other companies with less experience in this niche area. There is concern that this level of offline disruption may re-occur and mimic the disruption presented in this study on an international scale.

Conclusions and Recommendations

Average response times below 300 ms are realistic and achievable under FMD conditions [13]. Therefore, average response times should not undermine MA effectiveness. However, offline issues may be linked to incorrect quarantine and are likely to have caused significant delays and confusion during offline periods. Hospitals and pharmacies are suggested to review their dispensing SOPs to include guidance regarding medicine dispensing operations during offline periods and record offline periods as a risk on their risk registers. They could also mandate that their technology providers build in explicitly clear alerts that describe precisely what is required during offline periods and match those alerts with clear internal guidance, Standard Operating Procedures (SOPs) and training. Although this technological approach has proven its ability to operate at average response times well below the FMD mandated limit of 300 milliseconds, it is suggested from this study that offline issues may have an

effect on incorrect quarantine and that offline issues are likely to disrupt the delivery of medicines to patients. One way to reduce offline issues would be to penalise the National Medicines Verification System (NMVS) provider for offline instances beyond an agreed contracted level. With appropriate incentives, NMVS providers may be more likely to prioritise and rectify offline incidents.

It is important to be aware of the value of medicine serialisation and decide if an organisation wishes to grasp additional value or settle for the minimum level of legal compliance. It is suggested that pharmacy regulatory bodies in countries with medicine serialisation legislation, should provide clear guidance concerning the sanctions associated with failure to decommission a medicine according to EU FMD legislation.

Figure 1.0: A diagram identifying the total number of medicines included in both studies

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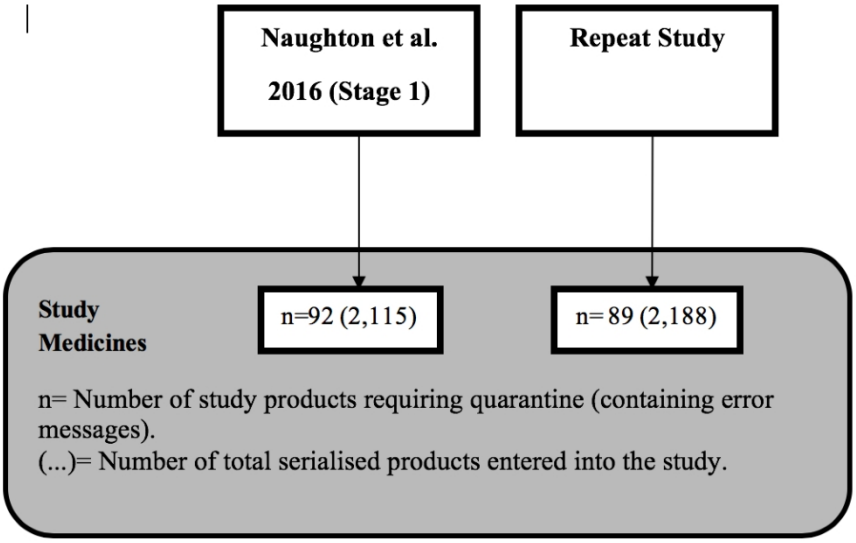

Figure 1.0: A diagram identifying the total number of medicines included in both studies [13].