



Case study

The Future of Falsified and Substandard Medicine Detection: Digital Methods To Track and Authenticate Pharmaceutical Products

Background Paper

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1. Introduction

An example to demonstrate the history of fake medicines relates to records from post-World War II Berlin and Vienna, where fake penicillin was being manufactured and sold, or stolen, from hospitals and diluted (Newton and Timmermann, 2016). Vials of glucose liquid and used penicillin bottles were filled either with crushed antimalarial tablets or face powder and sold for \$300 and \$375, respectively - amounts equivalent to \$3900 and \$6400 today (Newton and Timmermann, 2016). Supply issues and consumer demand, aided by the societal disruption caused by the war, made such crime possible. The situation created an opportunity for criminals to manufacture a fake product in illegal laboratories, and to sell it in illegal markets. And, to this day, the falsified medicines industry carries on, still driven by supply and demand.

Terminology in this conversation is important. The term 'Fake' is often used as a layman's term to describe counterfeit or falsified medicine (Isles, 2017). Historically the terms 'Falsified' and 'Counterfeit' were used interchangeably, however, in 2017 the WHO decided to rationalise the terminology and made a clear distinction between the two. The term counterfeit is a legal term which relates to IP infringements, therefore the terms 'Substandard and Falsified' have been adopted by the WHO to describe 'Fake' medicine (WHO, 2017). The WHO definition of a substandard medicine is 'Also called "out of specification", these are authorized medical products that fail to meet either their quality standards or specifications, or both', whereas falsified medicines are defined as 'medical products that deliberately/fraudulently misrepresent their identity, composition or source' (WHO, 2017).

Internationally, concerns regarding substandard and falsified (SF) medicine are growing. Many studies identify cases of SF medicines in low- and middle-income countries (LMIC) in Asia and Africa (Nayyar et al., 2012; Binagwaho et al., 2013; Kaur et al., 2017). However, this issue is not isolated to LMIC's. Between 2001 and 2011, 11 cases of falsified medicines were identified in the UK (Almuzaini et al., 2013). Arguably the most famous case of an SF medicine in a high-income country (HIC) surfaced in the United States when falsified versions of the multi-billion-dollar cancer drug, Avastin, were distributed; the fake drugs lacked the active ingredient, and, instead, contained products such as corn-starch, salt and acetone (Mackey et al., 2015). Moreover, multiple cases have emerged in which medicines purchased online have been identified as falsified (Orizio et al., 2011), and, as online purchasing increases, the purchase of falsified medicine may also grow.

The prevalence of substandard or falsified medicines in any given country is difficult to document. Many studies that research this phenomenon face funding restrictions, and use sample sizes too small to produce generalisable results. Despite limited data, the World Health Organization (WHO) has published a report which indicates that 10.5 per cent of medicines in low- and middle-income countries are identified as substandard or falsified (WHO, 2017). A model in the report estimates the potential impact of these fake medicines. For example, the model shows that up to 72,430 deaths from pneumonia among children ages three to five years old can be attributed to the use of substandard and falsified antibiotics that had reduced antibiotic activity (WHO, 2017). If the SF medicines lead to the use of drugs with no antibiotic activity, this figure increases to 169,271. (WHO, 2017). The report also estimates that the reduced effectiveness of SF medicines leads

to an additional 529 deaths from malaria per 1 million cases seeking treatment. In sub-Saharan Africa alone, such medicines contributed to an additional 72,000-267,000 deaths annually, with an estimated cost of between US\$12.1 million and US\$44.7 million spent on additional treatment and care (WHO, 2017). A systematic review of online pharmacies found that the prevalence of poor quality medicine purchased online ranges from 2.5 per cent to 62 per cent of all drugs purchased through the Internet (Orizio et al., 2011). However, the prevalence of falsified medicines varies from country to country, and changes continually, depending on the unique context within a given country, or at its borders, at any given time. The rate of medicine falsification can fluctuate for many reasons, such as a change in the perceived risk of retribution, or shortages of legitimate medicines.

The WHO prevalence figures are generally regarded as the best available measure of the extent of this fluid, international issue. SF medicines are an example of a 'Wicked Problem' which requires collaborative action with strong leadership (Grint, 2010). As its 2017 report concludes, 'If governments and other decisionmakers increase their efforts and resource them appropriately, the rising tide of falsification can be reversed and quality standards increased globally to ensure that people all around the world have reliable access to medical products that work as they are supposed to' (WHO, 2017).

2. The Medicine Serialisation and Authentication Processes

Against this backdrop, countries are considering what steps to take to address the problem of counterfeit medicines. Among the most prominent efforts are new medical authentication systems scheduled to be used across Europe in early 2019, and a similar system for the United States that is to be fully implemented by 2023.

A cornerstone of these planned efforts, and efforts underway elsewhere, is medicine serialisation, that imposes a standardised identification number on medicines. Different countries are at different stages of medicine serialisation. A partial list of countries that have agreed to medicine serialisation includes the EU (European Commission, 2011), the United States (FDA, 2013), Argentina, Brazil, South Korea, India, China, and Turkey (Infosys, 2017) which are at a different stages of roll-out. Serialisation involves systematic printing of two-dimensional barcodes (commonly using GS1 standards) onto pharmaceutical products. Using a standardised barcode format allows for intranational and international interoperability, simplifying and reducing costs for all parties involved in barcode scanning. Serialisation is currently in place in some countries and is planned for others which is typically followed by either track-and-trace or end-to-end processes. Track-and-trace processes provide verification of a barcode upon transfer of ownership from one party to another, at every transaction. The end-to-end process involves the commissioning of a medicine pack at production and decommissioning (also referred to as authentication) of the medicine by a healthcare professional at the point of supply to the patient. In the United States, the Drug Supply Chain Security Act (DSCSA) is preparing for a track-and-trace solution, whereas in the European Union (EU), the Falsified Medicines Directive is preparing for an end-to-end solution.

3. The EU Example

The EU is currently preparing for full serialisation and medicine authentication by February 2019. Therefore these processes are currently in a state of preparation. In the EU, the barcode on a medicine packet includes the global trade item number (GTIN), expiry date, batch number and unique identifier. The unique identifier will allow for unit-level authentication of medicines. The EU end-to-end medicine authentication system will involve manufacturers sending data from the barcode of newly commissioned drugs to a central European hub, which has already been created. A copy of the data from this hub will then be directed to the national hub of the drug's expected destination (which is now in place in most EU countries), with medicines manufactured outside of the EU requiring repackaging and serialisation before being sold in the EU. Healthcare facilities will connect to their national hub to verify the information contained within each barcode, and to decommission the medicine to be dispensed. The medical authentication system will rely on a cross-checking database, which will allow a healthcare professional to identify whether the medicine they are dispensing is on the list of legitimate medicines held by the national database; whether the medicine has expired or been recalled; and whether the product code has been copied. Once scanned within the pharmacy, the medicine will be decommissioned from the national database, and any further attempts to decommission the same unique code will be alerted to authorities. Typically, the process of authenticating medicines will occur in community pharmacies, hospitals and the offices of dispensing general practitioner doctors. Some organisations such as the ambulance service, prisons, schools, care homes and hospices are exempt from the EU's Falsified Medicines Directive for practical reasons, and their wholesalers will be permitted to decommission medicines on their behalf before delivery.

4. The Use Case

The EU-legislated change of practice that is poised to being in February 9th 2019 will affect medical regulatory authorities, government healthcare agencies, and technology and pharmaceutical companies. However, healthcare professionals will perform the final, important step in validating the legitimacy of medicines for patients. This decommissioning step may involve front-line staff such as pharmacy technicians and pharmacists, doctors in specific clinics, nursing staff on hospital wards, and technical staff working in wholesale companies or hospital departments handling central stores. To reach the final goal of systematic medicine authentication before administration to a patient, systems need to be in place to facilitate medicine decommissioning. Current systems and processes within healthcare facilities, such as hospitals, dispensing general practitioners and community pharmacies, will need to be assessed to understand how the incoming practice change will fit amongst existing processes. Standard operating procedures within healthcare facilities will require updating to incorporate the incoming legislative and practice change. Staff members of all grades will require education and training which is specific to their role within the organisation. Finally, and arguably the most crucial aspect of digital preparation, is the piloting of the processes and associated technologies required to carry out medical authentication. This will establish the system's technical and operational sensitivity and specificity. The senior management team within a healthcare facility will be required to choose and purchase a technological solution that links its pharmacy to a national database of legitimate codes, fits in with their working operations, and complies with the EU regulations. The front-line healthcare professional staff will be required to scan the barcode on each medicine dispensed to a patient. If the medicine is identified as falsified, potentially falsified, recalled, or expired, an on-screen alert will direct the healthcare professional to quarantine the product. Within a community pharmacy, this process must be performed at the point of supply to a patient. However, a hospital can decommission a product at any point during which a drug is within its possession.

The digital medical authentication solution may adversely affect how quickly a pharmacy can deliver medicines to a patient. This is a key performance indicator for most UK organisations. The success of this process will be measured by its impact on surrounding processes, the impact on front-line staff, and, most importantly, the effective detection of substandard and fraudulent medicines. For this technological approach to be successful, users must be willing to be involved in shaping the change, which may include the identification of a local champion (Howell, 2005). The ideal process should authenticate medicines quickly, accurately, reliably, and in a user-friendly way. To reduce the impact on work processes, the most suitable practitioner should authenticate medicines at the most suitable point in the internal supply chain (Naughton et al., 2016).

5. Theoretical Benefits

The issue of substandard and falsified medicines is an example of a “Wicked Problem” (Grint, 2010). Solving this problem requires the co-operation of partners from a diverse group: governments and regulatory authorities; private industries such as pharmaceutical and medical technology companies; hospitals and pharmacies, healthcare workers, medical workers and their patients. Strong leadership is usually required to bring such a complex and wide-ranging array of stakeholders together. However, legislation is also an effective driver for this emerging technological approach, and it can provide the incentive for these organisations to co-operate effectively.

Although medicine serialisation and digital medical authentication systems were envisioned as tools to protect the public from the threats of substandard and falsified medicines, they potentially offer many other useful implications to the pharmaceutical industry and healthcare providers. The primary benefit to a hospital would be the improved identification of falsified, recalled and expired medicines. The serialisation of medicines allows for verification throughout the supply chain; thus, a hospital could use the data generated from product scanning to improve stock management and reduce medicine waste. Furthermore, the verification of medicine by nursing staff could form part of a broader medicines safety pathway. Such a pathway would involve the scanning of the patient's wristband, drug, and prescription - steps to ensure that the right patient gets the right medicine at the right time. Such a process could lead to reduced medication errors, as has been the result in the United States (Poon et al., 2010), and would contribute to the WHO 'Medication Without Harm' agenda (Sheikh et al., 2017).

For pharmaceutical companies, the serialisation and medical authentication process could reduce the legal and illegal movement of drugs from one EU country to another. This would improve pharmaceutical companies' ability to control the volume of stock within a given national market, and to manage drug shortages. Furthermore, if a company needed to recall a medicine for safety reasons, it would have the potential to recall part batches, which would reduce disruption to medicine supply.

6. The Oxford Pilot

A digital drug authentication study in line with the requirements of the EU Falsified Medicines Directive was conducted in Oxford between 2015 and 2018. To understand how digital drug screening would work in practice, the study simulated the environment and processes envisioned under the directive, using 'live' medicines with printed barcode labels. In the study, which involved the introduction of medicines into a working dispensary, 4 per cent of medicines generated a pop-up alert to identify a product requiring quarantine (Naughton et al., 2016). This study was unique in that it allowed researchers to track live medicines scanned by staff without compromising patient safety or medicine quality, as medicines labelled with error alerts were not substandard or falsified. This study included assessing the hospital's working operations, and liaising with users to understand the potential points where medicine decommissioning could be performed in the process. The study identified a technology response rate (time taken to verify the code against an external database) of between 152 milliseconds and 165 milliseconds which was within the 300 millisecond limit set by the EU FMD, without the observation of any false negatives. The study found that serialisation of medicines and digital medical authentication systems are technically sound, and as previously discussed, they provide additional potential benefits that go beyond compliance with the new legislation.

However, the study also showed that these approaches have obstacles. The technology yielded an authentication rate of 66 per cent (scanning compliance), and a detection rate of 53 per cent (products with alerts correctly quarantined). Considering the expected compliance rates should be approaching 100%, these initial results were poor. Compliance is a critical issue; without adequate compliance, valuable data are not generated, and unnecessary costs are incurred without reaping the full rewards. The UK has a history of poor digital project implementation in healthcare projects, with poor management strategy and poor stakeholder involvement playing considerable roles in previous failures (Hendy, 2005). Engagement of stakeholders and, specifically, front-line staff is important when implementing new technologies and altering working processes (New, 2015, Hendy, 2005). Without front-line staff engagement, implementation managers run the risk of developing processes that are unsuitable for the practice context. In the pilot study, better stakeholder engagement could have facilitated improved results. Stakeholder engagement links to Responsible Research and Innovation (RRI), which has also been referred to as 'Innovation + stakeholder involvement with regard to ethical and societal aspects' (Blok and Lemmens, 2015). Stilgoe et al., 2013 describe the concept as a combination of anticipation, reflexivity, inclusion and responsiveness; they, too, place importance on stakeholder engagement. The RRI concept can be useful in the development and integration of new IT infrastructure and related processes to build systems that are relevant to, and desired by, end users.

Other issues regarding medical authentication compliance relate to the software user interface, which includes the design of the alerts, and the functionality of the system used. The quality and effectiveness of digital alerts pose a real risk to digital healthcare compliance for medical authentication systems. A recent study found that issues relating to computer interfaces ranked highly amongst the obstacles to user compliance (Naughton et al., 2017). In this study, users of

the medical authentication tool in the Oxford pilot suggested that the visual appearance of alerts was important, and that audio alerts could also play an important role in identifying substandard or falsified medicines in specific contexts. However, more work is required to understand which alerts are most effective in digital health tools, as underscored by a Cochrane Review¹ that investigated the effectiveness of on-screen, point-of-care computer reminders (Shojania et al., 2009).

Context also plays a crucial role in digital implementation projects (Naughton et al., 2016). Each operational context within a healthcare facility differs due to unique systems and processes that have developed over years of practice, in response to service provision. Despite contextual variations, similarities do exist, and learning from similar implementation projects may prove useful.

Digital implementation projects take time and patience. They can be limited by the least motivated, capable or resourced partner. To integrate digital medical authentication tools into healthcare facilities, existing digital resources may require consideration to introduce the most efficient and valuable way to undertake the tasks. Incorporating these new technologies with existing software providers who are not incentivised to integrate poses an obstacle to progress. However, when integrated into a highly digitalised hospital, such technologies can add value to multiple areas of hospital operations. In this case study, the medical authentication technology was integrated with a pharmacy medication record system; such integration would facilitate the recording of the unique product code in patients' records, allowing for efficient patient-level drug recalls. Integration of medical authentication software into digital drug administration ward processes would afford hospitals the opportunity to provide nurses with the capability of verifying a drug whilst using barcode electronic medical administration record (eMAR) systems, which, in themselves, reduce medication errors (Poon et al., 2010). Thus, although integration with existing systems can be difficult, the value for highly digitised hospitals can extend beyond regulatory compliance.

Potential obstacles to the success of digital medical authentication technology require attention. Two main obstacles are poorly designed computer interfaces, and a lack of stakeholder engagement. A third issue relates to awareness. Most pharmacists in the UK are unaware of the issue of substandard and fraudulent medicines, and the implications of the incoming legislation to prevent their prevalence and use (Burns, 2017). This creates apathy towards the problem presented by counterfeit medicines, and this apathy can, in turn, compromise compliance with tools which aim to detect fake medicines.

¹ Cochrane Reviews, systematic reviews of primary health care research, are internationally recognised as offering the highest standards for evidence-based health care.

7. Medicine Authentication in Low- and Middle-Income Countries

Digital medicine authentication approaches similar to those presented in this case study could play an important role in the detection of SF medicines in low- and middle-income countries. This case study describes the issues that arise in a high-income country introducing a digital medical authentication approach to identify SF medicines. This case study did not identify issues that may surface in a developing-country context, such as access to digital technology services and implementation funding. The operational detection rate or user quarantine compliance of 52 per cent in the Naughton study was substandard, but this could be significantly improved with appropriate interface design and management strategies. This could facilitate the rapid, widespread and non-destructive detection of falsified medicines in low- and middle-income countries.

Pharmaceutical companies and technology companies in low- and middle-income countries would need to engage with medicine regulatory authorities to serialise pharmaceutical product lines for healthcare professionals to perform medical authentication. Smartphones and Internet access would be required to facilitate this agenda. In the past, such requirements would have presented considerable obstacles, but the rapid growth of smartphone use and Internet access in these regions may make their use more plausible (Aker and Mbiti, 2010; Poushter, 2016). Furthermore, the success of the serialisation and authentication approach may depend on national capacity, priorities and political stability – in addition to available or improving Internet access. The Oxford pilot could be reperformed in a hospital setting in a low- or middle-income country to understand the technical and operational obstacles to medical authentication in a different development context. The local context would need to be assessed to understand if any local constraints would hinder its implementation.

In high-income-country settings, organisations often focus on complying with regulations, and, as a result, they often fail to seek the full value from the medicine serialisation approach. Low- and middle-income countries offer a different context because of the higher prevalence of substandard and fraudulent medicines. With the prevalence of substandard and falsified medicines in low and middle income countries, now estimated to be 10.5 per cent, the matter of medical authentication may take on more urgency (WHO, 2017). The process may result in an initial compliance rate that is higher than the compliance rate seen in the Oxford pilot study due to a clearer need.

Organisational and cultural perspectives in developing countries must also be addressed. Therefore, the introduction of medical authentication technologies in low- and middle-income-country settings may also benefit from the previously mentioned RRI approach, which involves stakeholders and users in technology design and implementation to ensure the solutions are suitable.

Though smaller organisations may initially find implementation easier in low- and middle-income countries, larger healthcare organisations may reap the most significant rewards from effective implementation. Once governments and pharmaceutical companies see the value in the data generated by medicine serialisation, investment may begin to flow. As long as a standardised approach is used, harmonisation across continents is possible.

8. Summary

This case study and associated publications (Naughton et al., 2017, 2016) paint a picture of a technically sound, planned digital solutions to address the problem presented by substandard and falsified medicines, which appear to be growing internationally, particularly as purchases increasingly take place online. Evidence suggests that high-income country healthcare providers are largely motivated to implement new medical authentication procedures because of the legal obligations placed upon them to do so. By contrast, low- and middle-income countries may be motivated by the prevalence and urgency of the issue itself as falsified medicines appear, though an issue worldwide, to be more commonplace in low- and middle-income countries. Medical serialisation systems that rely on internationally recognised barcode information are already in place in many countries, and new technologies and legislations are poised to take effect. A medical authentication system is scheduled to be rolled out across Europe by February 9th 2019, and a similar system is scheduled to be implemented across the United States by 2023. Though differences exist, harmonisation across continents is possible so long as a standardised approach is used. Research has begun to explore the key elements that underpin successful implementation. Such research underscores the importance of proper user interface design, front-line stakeholder involvement, and incentives for implementation and compliance.

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