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REVIEW

A review of existing and emerging digital technologies to combat the global trade in fake medicines

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ABSTRACT

Introduction: The globalization of the pharmaceutical supply chain has introduced new challenges, chief among them, fighting the international criminal trade in fake medicines. As the manufacture, supply, and distribution of drugs becomes more complex, so does the need for innovative technology-based solutions to protect patients globally.

Areas covered: We conducted a multidisciplinary review of the science/health, information technology, computer science, and general academic literature with the aim of identifying cutting-edge existing and emerging 'digital' solutions to combat fake medicines. Our review identified five distinct categories of technology including mobile, radio frequency identification, advanced computational methods, online verification, and blockchain technology.

Expert opinion: Digital fake medicine solutions are unifying platforms that integrate different types of anti-counterfeiting technologies as complementary solutions, improve information sharing and data collection, and are designed to overcome existing barriers of adoption and implementation. Investment in this next generation technology is essential to ensure the future security and integrity of the global drug supply chain.

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Fake medicines; counterfeit medicines; substandard medicines; falsified medicines; health technology; anti-counterfeit; online pharmacies; supply chain

1. Introduction

1.1. Global trade in falsified and substandard medicine

The public health and patient safety threat of 'fake' medicines is a problem that has plagued the international community for decades [1–3]. As early as 1988, the United Nation's specialized international health agency – the World Health Organization (WHO) – recognized the urgent need to develop programs to detect and prevent the import, export, and smuggling of a host of dangerous medicines, including those categorized as substandard, falsely labeled, unapproved, counterfeit, and falsified (see Table 1 for definitions) [4–7]. Close to 30 years later, the global trade in fake medicines (which WHO recently limited to the terms 'falsified' and 'substandard') continues to be robust [8]. Varying estimates indicate that millions are potentially at risk from this form of globalized pharmaceutical crime that has matured into a multibillion-dollar industry endangering patients in high and low-income countries alike [9–11].

The dangers posed by falsified and substandard medicines have been detected throughout the global drug supply chain including in brick and mortar pharmacies, healthcare facilities and clinics, informal markets, drug wholesalers and traders, and via sale on the Internet [1,12,13]. The impact of these 'fake' medicines is enormous, as they inflict significant negative impact on patients' safety and treatment outcomes, lead to waste, diversion, and fraud and abuse in medicines access and healthcare financing, loss of confidence and commercial value of pharmaceutical brands, decrease economic output for communities impacted, contribute to the growing global threat of drug resistance, and have also resulted in documented patient deaths [1,4,9,12,14–18]. From a population health perspective, failing to address the deleterious impact of fake medicines can severely jeopardize progress and billions of dollars invested in development assistance for health, often delivered through large-scale international aid programs aimed at ensuring equitable, safe, and life-saving access to essential medicines [12,19–21].

Reflecting the enormous scope of the problem, close to 1000 different medical products have been reported as falsified or substandard to the WHO alone, including medicines across all major therapeutic categories and those that are both generic and branded/innovator products [10]. Additionally, a study that analyzed data collated by the Pharmaceutical Security Institute (a nonprofit, membership organization of pharmaceutical company security directors) from 2009 to 2011, found that there were over 1500 fake medicine incidents reported in the 'legitimate' supply chain (i.e. segments of the supply chain that are regulated and where patients should reasonably expect to receive an authentic product) across 69 different countries [22]. There has also been a substantial surge in the number of journal publications on the subject, indicating increased attention from researchers, funding agencies, and the broader healthcare community [23,24].

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Article highlights

- Our multidisciplinary review uncovered 60 articles from various disciplines describing digital technologies, solutions, and innovations in the fight against the global trade in fake medicines.
- The most mature digital anti-counterfeit technologies included mobile and RFID-based solutions, both of which use their underlining communication technology platforms to enable more robust fake drug detection, authentication, and track and trace.
- Less mature technologies, such as the use of machine learning, have yet to be sufficiently commercialized, but show great promise in detecting and preventing the sale and distribution of fake medicines especially via online venues.
- Blockchain stands out as a potential revolutionizing technology framework to better ensure a modernized and 'digitized' drug supply chain that is more trustworthy, accountable, transparent, and protected from fake drug infiltrations.
- While investment in anti-counterfeiting solutions to combat fake medicines is growing, leveraging the existing policy, legal, and governance environment to translate these technologies into action is critical.

This box summarizes key points contained in the article.

However, even with increased research, advocacy, surveillance and concomitant efforts by regulators and law enforcement to combat fake medicines, the true scope and impact of this global drug safety challenge remains underrepresented as incidents go undetected, are reported to the wrong agencies, or kept from the public record by national governments and/or pharmaceutical companies due to political or commercial concerns [16,21,22]. Key risk characteristics of the fake medicines trade are also inherently difficult to measure given its multijurisdictional nature, politicization of the issue, disagreement on terminology, the complexity and interconnectedness of manufacturer–supplier–consumer networks, and the constant evolution of the drug supply chain including its rapid globalization [4,6,16,25].

1.2. Globalization of the drug supply chain

Explosive growth in pharmaceutical spending has coincided with the globalization of the drug supply chain [6,26,27]. The structure of the modern pharmaceutical supply chain reflects an industry that is now transnational, interconnected, complex, and becoming increasing digital. Over the last two decades, pharmaceutical development, manufacturing, packaging and delivery has become dramatically more extended, globally dispersed and virtual in nature [6,12,28,29]. This process of globalization has introduced suites of new players in different international markets including contract based suppliers, manufacturers, suppliers of raw materials (i.e. active pharmaceutical ingredient), and trading partners resulting in a 'diversification' of supply networks [28,29]. This means that medicines constantly change hands and undergo multiple transactions between production and dispensing to the end-user patient, with each transaction increasing the risk for falsified and substandard products infiltrating the supply chain [6,12,22].

Though many global medicines supplier networks are interconnected, not all markets share the same risk characteristics or points of vulnerability [28]. For example, in high-income countries such as the United States, a smaller number of larger firms manage distribution of the wholesale drug market, resulting in most patients getting their medicines from large suppliers that deliver legitimate pharmaceutical products to licensed retail and hospital pharmacies through a controlled and highly regulated supply chain [30]. However, a smaller percentage of medicines also traverse through the largely unregulated 'gray market', populated by secondary wholesalers, traders, and resellers, where the possibility of sourcing improperly stored, diverted, contaminated, counterfeit or falsified medicines substantially increases [30–33]. Such was the case in 2012, when fake versions of the anticancer drug Avastin®, were purchased and likely administered to thousands of patients around the USA [34–36].

Conversely, in low-and lower middle-income countries, multiple drug supply and delivery systems often run in parallel within a country resulting in corresponding variation in efficiency, quality and oversight [12,37,38]. Hence, low-income and poor or limited resource settings may be more susceptible to fake medicines due to underlying challenges of lack of good governance in national pharmaceutical systems, weak drug quality and regulatory systems, and corruption in the health sector [37,39–42]. For example, substandard and falsified versions of antimalarial treatments are endemic in many resource poor areas, such as Southeast Asia and sub-Saharan Africa (where studies have estimated that as high as 40–50% of antimalarials may be counterfeit) directly contributing to hundreds of thousands of

Table 1. Categories and definitions of drug product quality and authenticity.

Terminology	Definition
Substandard	Substandard medicines are produced by genuine manufacturers but do not meet quality specifications set for them by National standards and/or National Regulatory Authorities. Substandard medicines are usually the result of poor manufacturing or manufacturer storage practices; however subpar product quality can be caused by other drivers as well. For instance, degraded medicines also fall under this category and include genuine drugs that are degraded and become poor quality by poor storage or handling conditions after leaving the factory
Falsified (previously counterfeit)/falsely labeled/spurious	Falsified medicines are deliberately and fraudulently produced or mislabeled with respect to identity and/or source. Falsified medicines can include both branded and generic medicines. These products can include the incorrect amount of ingredients, wrong ingredients, no active ingredients, have insufficient quantity of ingredient(s) or be packaged incorrectly/fraudulently.
Counterfeit	Counterfeit medicines are those that do not comply intellectual and industrial property rights, such as registered trademarks or patent rights
Diverted	Diverted medicines are genuine medicines that have been removed or stolen from legitimate markets and sold in unintended markets or gray markets fraudulently

preventable deaths, exacerbating disease burden, and contributing to a rise of resistant strains [20,43–46].

1.3. Digital 'gray' market

Globalization of consumer markets coupled with the rise of e-commerce platforms has also resulted in new channels that fake medicines can penetrate, including purchase and delivery via the Internet [47–51]. Specifically, the accessibility, anonymity, low-cost, and global reach of Internet-based technologies has enabled the rapid proliferation of online pharmacies (estimated as more than 35,000 websites), or more simply websites that purport to operate as legitimate pharmacies via the Internet or mail-order and sell prescription drugs direct-to-the-consumer [51–53]. However, the vast majority of these online 'pharmacies' conduct business illegally and without appropriate safeguards, including not requiring a valid prescription, operating without a valid license/certification, and failing to meet national or international pharmacy regulations [49–51,54–56] These illicit or 'rogue' online pharmacies pose a serious threat to global patient safety as they act as a source and distribution point for medicines of questionable quality are not subject to the regulatory safeguards of the controlled supply chain, and lack clinical oversight from a clinician/physician, pharmacist, or other trained healthcare professional [51,57].

When consumers purchase medicines from illegal online pharmacies, they become active participants in circumventing a regulatory system designed to protect the safety, quality, and appropriate use of prescription drugs, while also creating broader market demand for the global manufacture, distribution and spread of fake medicines [9,47,51,58]. Consumers also face cybersecurity risks such as financial fraud, data phishing, and infection by computer viruses/malware/spyware that can add to existing health-related harms [51]. Hence, the globalization of e-commerce has enabled the creation of a 'digital' pharmaceutical gray market completely separate from the legitimate supply chain, but in many ways, more convenient though equally dangerous. Importantly, ongoing challenges regarding ensuring equitable access and affordability to prescription drugs remain driving factors in perpetuating this alternative avenue of demand and sourcing [12,16,59,60].

1.4. 'Digital' supply chain solutions

As physical and digital vulnerabilities remain exposed, different methods of ensuring the integrity of the global drug supply chain are needed to address the unique challenges posed by different international markets, supply chain dynamics, and legal jurisdictions. Primarily, fake medicines countermeasures have relied upon serialization (i.e. identifying a medicine by using unique printed codes, images, or holograms on packaging to verify authenticity), authentication (i.e. scanning a medicine product at point of supply through to the patient to verify authenticity), and track and trace technology (i.e. logistic technology that follows the current and past locations of medical products through the supply chain) [18,45,61,62].

While these solutions can be effective, advances in information science, software development, and web-enabled technologies are transforming security for electronic transactions and supply networks of other industries (such as in the financial technology and e-commerce sectors). These same emerging 'digital' technologies are also increasingly being used to improve performance, management, and interoperability of the global pharmaceutical supply chain (including use of IT infrastructures, data analytics, inventory management, and end-to-end supply chains) yet have yet to be fully leveraged to detect and prevent fake medicines [63].

Despite advances in many digital technologies, the potential application and translation of these solution to address the complex drug safety challenge of fake medicines is only beginning to take shape. This despite growing importance for a digital 'modernization' of the drug supply chain, given that 3.5 billion people are now connected to the Internet and 95% of the world is connected to a mobile cellular network [64]. Importantly, these technologies may hold real promise in turning the tide in the fight against the fake medicines trade by tackling supply chain vulnerabilities, but more in-depth assessment is needed to identify opportunities and barriers to their realization.

2. Methods

2.1. Aim

The aim of this review was to identify existing and emerging digital technologies designed to ensure the integrity of the global drug supply chain by combating fake medicines. We undertake this review to better understand how digital technologies can enable cooperation and coordination among different international stakeholders to address a decades-long public health problem that demands innovative solutions in order to protect patients globally. We note that we did not include discussion about traditional forms of anticounterfeiting technologies that do not specifically have a digital technology application (e.g. product serialization, use of packaging authentication, visual inspection solutions, laboratory or forensic detection technology including but not limited to x-ray powder diffraction, spectroscopy, nuclear magnetic resonance, infrared imaging, and liquid chromatography) as these countermeasures have been extensively covered in a 2014 review article published in PLoS One by Kovacs et al. [45] We also did not focus on the review of policies related to public health interventions or health system-level interventions (i.e. regulatory measures, public education/awareness, and pharmacovigilance) as this has been previously examined in systematic review articles by Hamilton et al. in Health Policy and Planning and Fadlallah et al. in Pharmaceutical Medicine respectively, both recently published in 2016 [17,58].

2.2. Literature review

We first conducted a literature review for journal articles, original research, conference papers, case reports, technology reviews, commentaries and news reports that were indexed in four scholarly databases. This included conducting search term

queries on the databases PubMed (Medline), IEEE Xplore, ACM Digital Library, and Google Scholar. The rationale for choosing these databases was the interdisciplinary nature of the study aims, which required a review of the science/health literature (PubMed-indexed journals that cover life sciences and biomedical topics), studies on information, communication and engineering technologies (IEEE Xplore-indexed articles that focus on scientific and technical content published by the Institute of Electrical and Electronics Engineers [IEEE]), research on advances in computing sciences (ACM Digital Library indexes various journals, conference proceedings, technical magazines, newsletters and books in the computing literature), and a general search of the literature (Google Scholar indexes a variety of peer review papers, theses, preprints, abstracts, and technical reports for a variety of disciplines).

We limited our searches to English-language articles published between 2010 and 2016. Our search queries included the combination of two keyword categories: (a) terms associated with fake medicines and online pharmacies; and (b) terms associated with emerging 'digital technology'. We define 'digital technologies and solutions' as those that are: (1) enabled by Internet-based technologies and/or platforms (e.g. online portals and management systems, Internet-based supply chain tools, cloud-connected databases, social media-based applications); (2) use mobile or wireless technologies (e.g. mobile phone applications or wireless transmitting devices that connect to the Internet); (3) use of algorithms or other advanced computational methods for data analysis; and (4) solutions that share common IT-platforms, web connected databases or utilize cloud-based systems.

Keywords were queried in the Title/Abstract field using advanced search function settings for PubMed, IEEE Xplore, and ACM Digital Library databases. For Google Scholar, we used natural language queries limited in time frame of published date and excluded results of published patents. We chose a 6-year literature review period as this study is focused on relatively new, emerging, or innovative technologies and based on findings indicating that published literature on the subject has increased at the highest rate over the past 5 years [24]. A visual description of how we conducted the literature review and the keywords used are provided in Figure 1 and detailed below.

After our initial search results, we applied an inclusion and exclusion criteria that filtered results by reviewing abstracts of extracted articles. We first excluded articles that did not discuss application of technology to fake medicines (e.g. discussed other fields of study or other counterfeit goods such as consumer products, currency, electronic components/equipment, cosmetic products, foods, cigarettes, or dietary supplements) and then excluded articles that included fake medicines but did not discuss forms of digital technologies and solutions (e.g. laboratory-based technologies not connected to the Internet, survey instruments or analysis of secondary data, discussion of professional guidelines and/or recommendations, policy and regulatory related topics, and traditional forms of packaging authentication and serialization).

In order to expand our search and capture emerging and new technologies that may have been absent or not extensively covered in the academic literature, we also reviewed gray literature sources using structured natural language web searches with a similar combination of keywords on the popular *Google* search engine. We retrieved and reviewed information sources including technical reports, reports from government agencies, news reports from media outlets (i.e. nonscientific sources), company websites, blogs, and press releases, information from nongovernmental organizations/trade associations/solution providers/supply chain companies, and information from government and regulatory agency websites. We specifically focused on existing and emerging technology already identified and/or referenced in our academic literature review (e.g. specific types of technologies, names of companies, names of solutions) and reviewed results carefully to identify case studies, updates, and other supplemental information. Gray literature searches were conducted from November 2016 – January 2016 and were limited to the first five pages of results for each keyword search query combination.

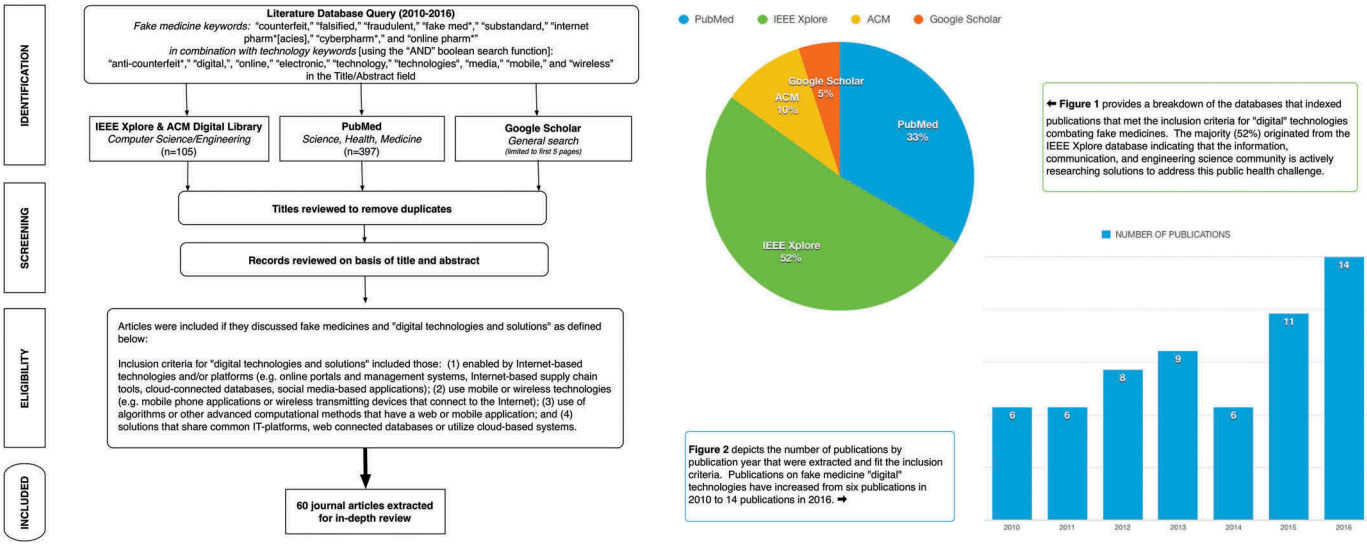

Figure 1. Literature review search methodology and characteristics.

3. Results

Our review of the literature identified five distinct categories of 'digital' technology solutions and platforms that are either existing or emerging in the fight against fake medicines (see Figure 2 for summary). Overall, the most mature of these digital technologies were the categories of mobile solutions for fake medicines authentication and tracking, the use of Radio-Frequency Identification (RFID) coupled with other digital tools to better secure the drug supply chain, and the development of web-based platforms to better verify legitimate versus illegal online pharmacies. It is notable that solutions within this first category of technology all have commercially viable applications. Outside of these more established technology formats, other solutions such as the application of machine learning, advanced text processing, and blockchain technology, are still in their emerging phases, where experiments, conceptual designs/frameworks, use cases, and early-stage technology was predominant, though research and investment appears to be growing. Collectively, emerging digital technologies are at varying stages of maturity and mainly target pharmaceutical companies, governments (e.g. drug regulators, customs officials, law enforcement), and pharmaceutical manufacturers and retailers, though end-user patients are growing as a potential user base. Below we detail each technology category and provide select case studies illustrating their practical application.

3.1 Mobile technologies

Few technologies are as globally ubiquitous as the mobile phone, which now commands approximately 3.6 billion global mobile-cellular subscriptions [64]. Given the widespread presence of mobile phones in both developed and developing economies, wireless or mobile driven solutions to protect consumers against fake medicines appeared to be among the most mature, and are particularly promising given their potential for scalability and user adoption. Primarily, these solutions seek to leverage the growing capabilities of mobile phone device platforms, software, built in sensors, cameras, and ability to connect to GPS, wireless networks and the Internet, by using mobile technology as a complementary solution to existing anticounterfeiting technologies.

Our review of mobile technologies identified six key commercial solutions that approach the problem in different ways but all share a mobile platform as a unifying technology backbone (see Table 2). These mobile technologies span from authentication services, track and trace solutions, and pill image recognition tools. Many of these technologies have launched within the past decade coinciding with increased uptake and advances in mobile features; with technologies such as *mPedigree's* launching as early as 2005 to the more recent market entry of *Authenticateit* in 2016 [65].

Among the six companies identified in this space, five used a form of mobile authentication and/or mobile-based track and trace solution (see Sproxil **Case Study #1** in Supplemental data). Furthermore, most companies had pivoted from original models of product serialization (e.g. scratch-SMS solutions) to supplementary security-as-service solutions that track medicine products across the supply chain [33,65,66]. An exception to this, and a leader in this context was the mPedigree platform, which from its early launch, used product serialization in combination with an electronic pedigree (e-pedigree) for increased security enabling verification of both product and transaction integrity [66–68].

In addition to the case studies of commercialized technologies reviewed, several research papers described experimental or proof-of-concept studies aimed at leveraging mobile platforms to develop higher-throughput, lower cost, and more user-friendlier authentication and track and trace

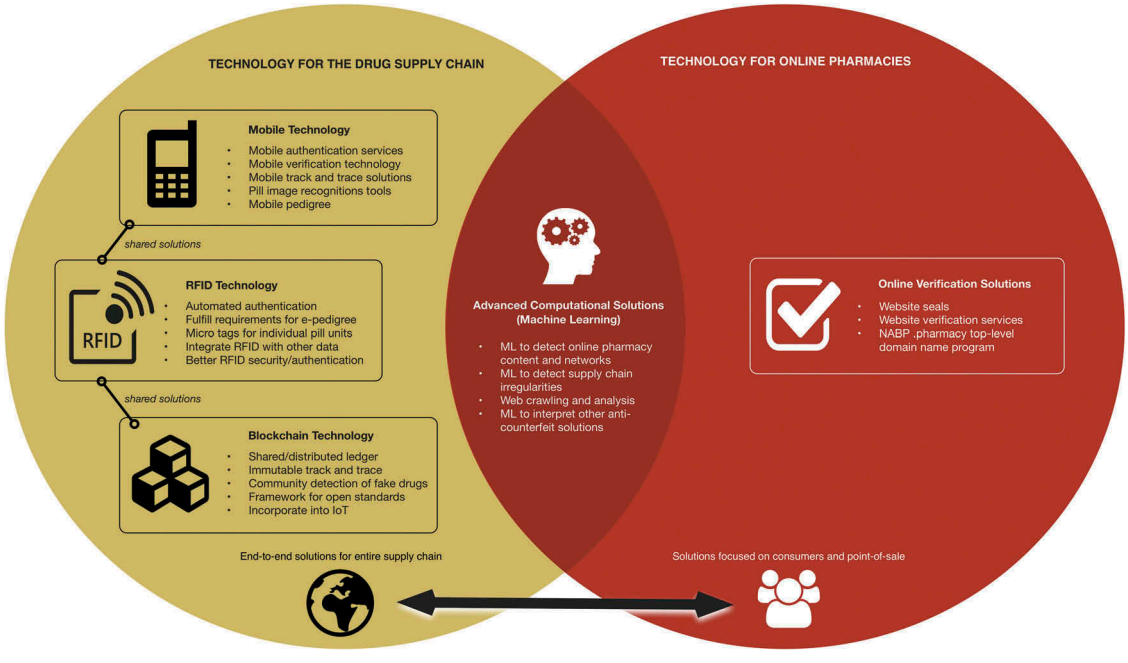

Figure 2. Visual summary of existing and emerging categories of digital technologies to combat fake medicines.

Table 2. Categories and definitions of drug product quality and authenticity.

Mobile Products	Description provided in the literature	Reach	Services			Key stakeholders
			Point of sale authentication	Supply chain authentication	Supply chain coordination	
Sproxil *[Founded 2009]* 	Sproxil is a mobile product authentication solution. Enables verification by using a mobile phone, QR code on the product and a free text message. If a fake product is found, consumers are also given a hotline number to call in order to report the fake product, so the issue can be directed to the appropriate authorities	20 million verifications[1]	x		x	Pharmaceutical, governments, distributors, retail outlets and patients
mPedigree *[Founded 2007]* 	mPedigree is a mobile pedigree identification record and product authentication solution powered by a cloud-based system offered by Hewlett Packard. mPedigree refers to mobile short code platform (using QR codes and barcodes) to interconnect GSM mobile networks via a central registry wherein pedigree information of product brands belonging to participant manufacturers are stored. mPedigree also offers other supply chain security and coordination solutions for retail pharmacies	10 million packs of medicine[2]	x	x		Pharmaceutical, governments, distributors, retail outlets and patients
PharmaSecure *[Founded 2007]* 	PharmaSecure is a mobile product authentication solution focused on end-user verification. Medicine packets are linked with a unique code (customized to market and regulation including alphanumeric barcodes etc.). Customers who purchase the drug can then text message that code to the PharmaSecure number and receive a response (voice, web or text) that authenticates the medication and provides expiration dates and related information. More recently, distribution wide services have also been provided	40 countries, 60 pharma companies[3] 500 m units of medicine secured[4]	x	x		Pharmaceutical, retail outlets, and patients
Epothecary *[Published 2009]* *No image available*	Epothecary is a mobile product track and trace supply-chain security solution proposal that uses camera phones to scan unique 'glyphs' attached to each medicine unit, at each level of packaging, distribution storage, and sale via SMS verification. This solution can also track quantity sold and GPS coordinates of the products across the supply chain	NA	x	x	x	Pharmaceutical, distributors, retail outlets and patients
MedSnap *[Founded 2011]* 	MedSnap is a mobile medicine image recognition that takes images via phone of actual pills and runs it across their authentic pill image library to provide a wide range of information and verification of the product	NA, commercially available	x			Governments and patients

(*Continued*)

Table 2. (Continued).

Mobile Products	Description provided in the literature	Reach	Services			Key stakeholders
			Point of sale authentication	Supply chain authentication	Supply chain coordination	
Authenticateit *[Expanded for Medicines 2016]*	Authenticateit is a mobile product track and trace consumer and supply-chain security solution. The Authenticateit smartphone app will enable clinicians and patients will scan products	NA	x	x	x	Pharmaceutical, governments, distributors, and patients

Sources:
[1]Sproxil Surpasses 20 million Verifications, 2015, available at: https://www.sproxil.com/blog/sproxil-surpasses-twenty-million-verifications
[2]mPEDIGREE, 2013, available at: http://www.africanstrategies4health.org/uploads/1/3/5/3/13538666/mpedigree.pdf
[3]PharmaSecure, About Us, 2016, available at: http://www.pharmasecure.com/about-us/
[4]Chabra E. Source Code: PharmaSecure Goes Mobile in Battle Against Fake Drugs. 2013; available at: https://www.theguardian.com/global-development/2013/may/09/source-code-pharmasecure-fake-drugs

solutions. This includes solutions that use mobile phone applications to authenticate and track individual medicine capsules using upconversion 3D fluorescent QR codes, Android mobile applications that enable consumers to check the regulatory status of medicines with the Ministry of Health, and a proposed mobile technology medicine verification framework using a data matrix to mitigate security vulnerabilities of existing commercial solutions [66,69,70].

Importantly, mobile phones can act as the primary device for integration with other physical platforms enabling image capture and data processing through cameras and software while simultaneously connecting these platforms to the Internet or cloud-based services to conduct real-time authentication and analysis of drug specimens [71,72]. This includes the concept of Mobile Product Authentication (MPA), where short message services (SMS), image capture, and code scanning can allow authentication of medicines by validating information hosted on cloud technology or other secured connected databases [65]. An example of this type of innovation included a proof-of-concept 3D-printed cradle that holds a mobile phone running a special mobile software application that uses portable thin-layer chromatography analysis to identify falsified or substandard medicines via image capture [71,72].

Advantages of using mobile-based authentication and track and trace solutions include that they require less infrastructure, are more cost-efficient to scale, can be more user friendly, can provide real-time analysis when connected to cloud databases, are already wireless and/or GPS-enabled, and have the potential to engage patients as participants in a collective security solution [67,73]. Furthermore, mobile track and trace technologies can provide benefits beyond securing the drug supply chain including reduction in medication errors, automated pharmacy billing and refills, and support for product recalls [18]. Recognizing these benefits, the Nigerian Ministry of Health mandated pharmaceutical companies (selling antibiotics and antimalarials) to implement a form of mobile authentication in 2013; similar legislation has also been introduced in India [18,74,75].

However, even with its considerable benefits, scaling mobile solutions to effectively combat fake medicines relies heavily on: (1) regulatory mandates for manufacturers to participate; (2) adoption of technology by different users/data points in the supply chain; (3) awareness and willingness of pharmacists to engage and educate supporting these solutions; and (4) raising overall consumer awareness about fake medicines to increase user participation. Additionally, while the proliferation of mobile authentication solutions has the short-term benefit of empowering more actors across the supply chain, there are also risks of having multiple privately owned authentication solutions serving the same market and lacking sufficient interoperability [76]. More specifically this could cause fragmented documentation, unreported cases of fake medicines from pharmaceutical manufacturers, and multiple and disparate sources of data, similar to current challenges faced by the fragmented network of public health surveillance for fake medicines [1,16,22]. Finally, mobile verification in isolation does not prevent fraud and should not to be used in place of traditional pharmacovigilance or traditional post-market surveillance systems [12].

3.2. RFID-based solutions

Radio Frequency Identification (RFID) is a rapidly emerging technology in various industries and is becoming a mainstay in supply chain management, but has only recently become more widely embraced by stakeholders in the pharmaceutical supply chain [28,77,78]. At its core, RFID is a technology that uses electromagnetic fields to automatically track and identify items affixed with tags containing electronically stored information. Hence, RFID and related standards (such as electronic product codes [EPCs]), enable the tracking and management of inventory throughout the manufacturing and distribution process, while also allowing remote authentication that enables identification of falsified, substandard, and adulterated medicines, while also acting as a critical tool during product recalls [25,28,62,79,80].

Prior to RFID, the industry primarily relied on barcodes affixed to medicines packaging for authentication and tracking, a technology particularly susceptible to counterfeiting and limited in data storage capacity [28,33,46,81]. In contrast, RFID operates under a system where a tag (transponder) with unique identification information of tagged-objects (i.e. affixed to drug packaging) transmits information through radio waves or wireless channels to a reader (interrogator) that extracts data on the product/lot that are then captured and stored in computer/server systems or web portals [28,62,77,82]. Though several commercial pharmaceutical RFID solution providers exist, barriers to universal adoption include challenges associated with interoperability and integration across foreign firms, the need for standards setting, costs and time required for implementation, and questions about the utility of RFID IT investment [28,33,58,79,83]. These barriers exist despite legislative requirements in some countries that require forms of 'e-pedigree' (i.e. an electronic document that provides data on the history of a batch or lot of drugs enabling traceability and transparency) that may rely on RFID technology [28,46,58,77,79,84].

Novel approaches attempting to address some of the underlying commercial and technical challenges of RFID adoption are described in several studies, most of which were extracted from the IEEE database. These studies explore ways to improve the security, usability, and efficiency of RFID-enabled supply chains including: (1) protecting RFID from security and privacy breaches; (2) proposing systems to better integrate RFID information from pharmaceutical supply chain participants (including integration of RFID and EPC data); (3) development of algorithms using secure multiparty computing and differential privacy to secure e-pedigree; (4) creating micro RFID tags for individual pills or capsules (instead of affixing tags to packaging); (5) proposals to include temperature and humidity conditions in e-pedigree for cold chain management; (6) the use of centralized databases/systems for supply chain information transmission; and (7) developing more robust RFID authentication protocols and processes (including use of cryptography and Near Field Communications ('NFC') via mobile phones) [78,80–82,84–89].

Two distinct categories appeared to have the highest levels of research activity. The first category focused on creating lower cost, smaller, more resilient, safer, and edible forms of RFID tags that can be applied to individual tablets (versus packaging) to enhance security measures (see TruTag™ **Case Study #2** in Supplemental data) [79,88,90]. Another example was an experimental system that used 'chemometric authentication' using nuclear quadrupole resonance spectroscopy (a quantitative radio frequency spectroscopic technique) to both authenticate and verify the actual contents of medicines at various stages in the drug supply chain [90]. The second highly engaged category included RFID authentication solutions. These focused on mitigating vulnerabilities from security attacks against data transmission (including desynchronization attack, impersonation attack, reapplication attack, parallel session attack, modification attack, denial-of-service attack, and tag cloning), securing anonymity and untraceability, using batch authentication to improve process efficiency, and better securing mutual authentication [82,85,91,92].

Importantly, the majority of RFID solutions examined were aimed at improving and acting as complementary solutions to existing anticounterfeiting product authentication and track and trace strategies (e.g. imaging technologies, 2D-barcodes/QR codes, cryptography, mobile platforms, chemical fingerprints, etc.) by using RFID to securely transmit data and validate it over the Internet or in the cloud [79,88]. Hence, RFID shows promise as an underlying technology to better 'digitize' the global drug supply chain for the dual purposes of improving logistic performance and enhancing drug safety.

3.3. Advanced computational solutions

A separate category of anticounterfeiting solutions (reported primarily in the computer science literature) focused on the use of advanced computational methods for the detection and mitigation of cybercriminal activities, specifically including illicit online pharmacies and drug supply-chain incursions. Solutions were primarily grouped into two categories, most in conceptual, experimental, or proof-of-concept phase, including: (1) use of machine learning algorithms to better detect and classify illicit online pharmacies through text mining and content analysis; and (2) use of machine learning to detect irregularities or patterns of counterfeit penetration in the drug supply chain.

The development of machine learning algorithms applied to 'big data' is a growing field in many disciplines including health, medicine, and drug safety, and has formed the basis for a new research area known as and 'digital' surveillance or 'infoveillance' [93–98]. Specifically, machine learning is a subfield of computer science and a type of artificial intelligence that allows computers to learn without being explicitly programmed when exposed to new data. The machine learning utilized to address illicit online pharmacies focuses on training algorithms that can shift through large volumes of machine-readable content and automatically classify the content characteristics such as websites, email spam, and social media communications. This method is useful in detecting criminal activities that may follow certain distinct patterns or present as anomalies in a large set of data. Machine learning has also been used to address other diverse drug safety topics

including data on post market surveillance, adverse events, drug toxicity, and drug discovery [93,99–106].

The first category of studies used different applications of machine learning to detect illicit online pharmacy content and communications by identifying and classifying: (a) tweets (on the popular microblogging platform Twitter) promoting illicit online pharmacy sales of prescription controlled substances; (b) a framework for text mining Facebook and Twitter content to detect negative sentiment about drug products that may signal counterfeiting; (c) Internet and website network information and content level features (e.g. HTML text, images, network stack information, other metadata) indicating counterfeiting activities; and (d) cluster analysis that identifies large website networks involved in pharmaceutical cybercrime and spam [96,97,103,107,108]. Another study used human annotation (i.e. not machine learning) to analyze 'signal' data on website trust features (e.g. verification seals, store presence, product selection, fulfillment features, and health content) to accurately classify regulated versus unregulated online pharmacies, a method that potentially could be scaled if adapted for use with machine learning protocols [109].

Three particularly innovative studies combined web crawling (i.e. using crawlers/bots to mine content from webpages) and machine learning to detect and classify different actors in the online pharmacy ecosystem. The first describes a novel computational system named 'PharmGuard' that uses a web crawler and supervised machine learning algorithms to automatically identify search engine indexed online pharmacy websites and related advertisements [110]. Another study described the development of an adaptive learning algorithm called recursive trust labeling (RTL) that was tested to detect fake medical websites (including online pharmacies) and reported over a 90% detection accuracy when deployed over nearly one million websites [58,111]. A final study described a methodology that automatically extracts web page features for profiling online storefronts to train a classifier to accurately identify affiliate marketing programs that promote and spam information about online pharmacies [112].

A second category of machine learning technologies involved developing algorithms to detect fake medicines by mining data from the broader drug supply chain. This included an article describing a pattern-mining algorithm used in computer simulations to detect counterfeit medicines from track and trace records (such as RFID event data) [113]. Another study described the use of economic cybernetics to monitor differences in pharmaceutical supply flow to detect irregularities that could constitute fake medicine events [114].

In a completely different application of machine learning, deep learning models (a branch of machine learning based on artificial neural networks that has commonly been used in speech and image recognition) were used in combination with physical counterfeit drug detection devices, specifically Paper Analytical Devices (PADs) [115]. PADs are paper-based testing kits embedded with reagents that react with chemical compounds producing a set of distinctive color patterns that can be visually compared to stored images of authentic products indicating whether a drug is fake [115]. However, due to challenges faced by the need for human interpretation of results, Banerjee et al. developed an image recognition classifier designed to automatically compare PAD visual testing results to stored images of authentic drug PAD samples, with some models reporting high accuracy of classification models [115]. They also describe plans to develop mobile message services so users can send their PAD images in order to build a larger test dataset to improve their classifier models [115].

Though promising, advanced computational methods that leverage machine learning to fight online and physical distribution of fake medicines appear to lack sufficient investment as we were unable to identify a commercially available solution fully utilizing this technology approach. This despite machine learning underpinning several leading consumer platforms (e.g. video and music streaming services, web search engines, online advertising) and actively being used by several industries including the healthcare sector for other issues.

3.4. Online pharmacy verification solutions

Our review also captured four categories of web-based solutions designed to verify and educate consumers about the dangers of illicit online pharmacies. These technologies serve the purpose of providing consumers with reliable information about the legal status of an online pharmacy and whether it has been appropriately vetted by regulators in their country of operation. Technologies in this category include: (1) website seals; (2) commercially available website verification services; and (3) a new top-level domain name for legitimate online pharmacies. Different from other technologies reviewed, web-based solutions focus on protecting consumers at the point-of-sale, while also rely on consumer awareness, education and user participation in order to be effective.

The first category comprised of website seals, which are essentially images, links or objects displayed on pharmacy websites of accredited or legitimate online retailers. They are usually acquired through national, regional, or global agencies that provide a form of accreditation or certification of legitimacy and quality. The National Association Boards of Pharmacy (NABP) in the United States implemented the Verified Internet Pharmacy Practice Sites Seal or 'VIPPS' seal as early as 1999 in response to the rise in illicit online pharmacies [116]. The seal was provided to pharmacies via a rigorous application process, inspections/audits, and a recurring fee to participate in the program. Similarly, in 2015, the United Kingdom launched the EU common logo for all online pharmacies and retailers offering medical products for 'human use in the European Union' [117]. The UK common seal, like VIPPS is not intended to be used in isolation to verify website authenticity, but instead is activated when the logo is clicked and the user is redirected to a separate verification page. However, for website seals to be successful there must be existing consumer knowledge on the dangers of illicit online pharmacies, consumers need to be aware the seals exist and their purpose, and duplication or counterfeiting of online seals needs to be prevented.

A second category includes website verification services that comprise of large databases containing information about online pharmacies (usually collected through web crawlers) that enable consumers to check the status of an online pharmacy's by querying its URL. LegitScript LLC is a commercial leader in this space and partners with several private companies, including Google, Amazon, Visa, and Bing (Microsoft), to monitor and identify fraudulent online pharmacies. It also operates a website that allows free public searches so that consumers can check an online pharmacy's legitimacy via a searchable database [51,118,119]. However, not all website verification services may be reputable and they also require constant monitoring and updating as new websites are removed and created and as existing ones change or potentially become noncompliant [50,51,57].

An alternative approach to website verification services is one that is taking advantage of recent changes in Internet governance. In 2011, the Internet Corporation for Assigned Names and Numbers (ICANN) launched a new program to create thousands of new generic top-level domain (gTLD) names (i.e. the highest level of the Internet name space or simply everything after the final dot in a web address) including domains associated with health services (e.g. .health, .doctor, .medical) [120–122]. Included in the new gTLD proposals was an application for a .pharmacy domain with NABP as the registry operator. The .pharmacy domain's purpose is to act as a dedicated name space on the Internet to host legitimate online pharmacy websites and other related resources vetted through NABP's approval processes (see .pharmacy **Case Study #3** in Supplemental data for more details). Applications to apply for a .pharmacy domain are now available and if successfully adopted would act as a 'built-in' verification tool for online pharmacies by signaling to consumers that any website with a .pharmacy web address is legitimate [123]. However, many consumers are not aware of the new gTLDs, and it remains to be seen if legitimate online pharmacies will use this platform to market the credibility and safety of their services.

3.5. Blockchain technology

A final emerging technology category we identified was leveraging blockchain technology to combat fake drugs and dynamically enhance the security of the drug supply chain. Fundamentally blockchain is a secure distributed digital ledger (i.e. simultaneously shared across multiple users/locations and not stored in a single location) made up of 'blocks' of continuous transaction information. Blockchain technology has been the subject of widespread attention, investment, and industry hype, given its potential to share, sync, and better secure (through cryptography and 'miners' that validate and chain together blocks of transaction data without the need for a central authority) transaction information and data via a peer-to-peer, distributed and decentralized database structure [124–126]. Best popularized as the underlying technology for the cryptocurrency bitcoin, blockchain solutions can be used to record and authenticate transfers of information (including economic and supply transactions), execute of 'smart contracts', and operate an immutable, shared, and encrypted transaction ledger that can be used to track and trace goods across the supply chain [124–127].

In the context of fake drugs, the application of blockchain has the potential to: (1) track and trace pharmaceutical raw materials and finished product from manufacture to end user in an immutable and shared e-pedigree-based digital ledger; (2) provide greater transparency and enable detection of fake drugs in the supply chain by allowing blockchain participants to verify the authenticity of data; (3) integrate anticounterfeit devices into the 'Internet of Things' and better enable detection and authentication; and (4) could serve as an open standards technology to enhance information sharing across unrelated databases and different actors in the drug supply chain [127–129]. This could potentially transform a blockchain-enabled drug supply chain into a more trustworthy, accountable, and transparent shared and open data architecture that could cross multiple supply chain actors and jurisdictions.

Despite its potential to better establish drug supply chain provenance, we were only able to extract a single 2016 IEEE non-research article that summarized a few blockchain projects initiated by different organizations and explored it as a potential solution for fake medicines among other healthcare problems [125]. Though there was little literature on the subject, our review of the gray literature turned up several examples of prototypes, use cases, and research and educational initiatives for pharmaceutical supply chain-related blockchain activities. This included startup companies, such as Chronicled, Inc., which has launched prototype technology combining NFC embedded adhesive seals that are registered and verified on a blockchain, a project by iSolve, LLC that simulates how blockchain can be used to track medicines in a theoretical supply chain, a use case by BlockVerify for an anticounterfeiting platform using verification tags verified via blockchain technology, and the presentation of conceptual design and use cases by Rubrix by Deloitte (spun off from major professional service firm Deloitte Touche Tohmatsu Limited) [125,127–132].

Other examples of blockchain pharmaceutical supply chain initiatives included the multistakeholder BlockRx project to pilot blockchain technology in the pharmaceutical sector, the open source collaboration Hyperledger (backed by the Linux Foundation) to explore use of blockchain to improve pharmaceutical supply chain security, hackathon contests and boot camps that have featured conceptual solutions aimed at ensuring quality and accountability in the supply chain, and educational and outreach initiatives by IEEE Standards Association (including a virtual blockchain workshop and webinars) [125,132–135].

Though still in its relative infancy, the march toward commercialization of blockchain technology to address the fake medicines trade appears to be outpacing research efforts. This indicates that rapidly emerging technologies backed with strong private sector investments may bypass early stage research and experimentation typically reported in academic journals, though the success of blockchain to combat fake drugs remains to be realized.

4. Conclusion

Securing pharmaceutical supply and delivery networks in the age of globalization represents a significant challenge for governments, regulators, and pharmaceutical companies. However, without effective solutions, patients often bear the ultimate burden of poor quality and fake medicines at the cost of their health, finances, and sometimes with their lives [12]. As criminals become more sophisticated and supply networks more complex and diverse, new technologies to prevent, detect and respond to fake medicines need to undergo a continuous process of improvement, implementation and evolution in order to ensure drug safety in the twenty-first century [79].

Though our study focused on existing and emerging 'digital technologies', the majority of articles published on fake medicine solutions concentrated on traditional forms of laboratory and field-based technologies for detection and testing, medicines packaging authentication, and enhanced pharmacovigilance used to test products [7,18,58,61,69,79,136–139]. Though some of these 'traditional' solutions included cutting-edge innovation, including hand-held and/or portable laboratories (e.g. Portable Raman spectrometer, GPHF Minilab®, and US FDA CD3+ counterfeit device), molecular fingerprinting (including use of physical chemical identifiers and nanotechnology/nanoparticles), and fabrication of advanced anticounterfeit packaging using nano- or micro-materials, they did not meet our criteria of leveraging digital technologies that could enable them to be wirelessly/Internet enabled, networked, and better integrated into other anticounterfeiting solutions [45,61,79,140,141]. However, it is clear that these solutions remain critical tools in the fight against fake medicines, as they are complementary to digital solutions reviewed here.

In contrast, our review of existing and emerging 'digital' technologies points to an overall evolution in anticounterfeit solutions design and conceptualization and leads us to some key conclusions. First, many of the digital technologies we reviewed share a common characteristic: they do not operate in isolation. In fact, the underlining digital technologies they utilize (e.g. wireless, Internet, and radio-enabled capabilities) make them both ubiquitous and also acts to liberalize their platforms away from technology designed in isolation, as they share the ability to connect and interact with a whole array of information sources, devices, users, and stakeholders across the global drug supply chain. For example, digital solutions for pharmaceutical product authentication we reviewed have the potential to complement and enhance traditional security and anticounterfeiting measures (such as packaging authentication including overt and covert physical holograms or seals) by offering scalability, being more user friendly, acting in real-time, and being more cost-effective to deploy [62,73].

Further illustrating this point, mobile and RFID anticounterfeit solutions, the two technologies that were the most mature, serve as a digital backbone for other types of innovations. Mobile-based solutions primarily focused on leveraging the growing features and software capabilities of mobile phones to better enhance medicine authentication and expand track and trace along the spectrum from paper, electronic and now mobile pedigree solutions. Relatedly, at its core, RFID is simply a technology framework for automatic authentication and transmission of data that can be moderated by various forms of technology (including mobile and cloud-based applications), but also has the potential to act as a vehicle for more robust information sharing across different data points in the supply chain. Blockchain, albeit less mature, represents a potentially revolutionizing technology as it seeks to fundamentally change how stakeholders share drug supply chain information via a more trustworthy, secured, and accessible distributed and decentralized digital ledger.

Another key observation was that many of these new technologies were specifically designed to overcome existing barriers of adoption and implementation faced by traditional anticounterfeit technology. Many forms of anticounterfeit technologies have failed to scale due to inherent limitations such as the high costs of lab-based methods, lack of standards on testing for products, and a dearth of durable versions of these technologies needed for field deployment [23,24,45]. In response, many of the digital anticounterfeiting technologies reviewed were designed to specifically address these limitations by using lower-cost components, lowering equipment and infrastructure costs (such as using existing mobile phones and cellular networks in lieu of a complete device architecture), and using machine learning to automatically analyze large amounts of data with minimal human interaction. Technologies, such as web verification services and mobile solutions, were also designed to overcome adoption barriers experienced by end-users by educating and engaging the public in the fight against fake medicines. Despite potential advantages, commercialization of many of these solutions is still in its infancy, with ongoing questions regarding utility, cost-effectiveness, and the lack of incentives (such as legal or regulatory mandates) likely hindering greater investment.

Finally, though digital technologies have the potential to lower costs, enhance supply chain performance, optimize information capture and data transmission, and offer users greater convenience, they also carry the potential for increased security vulnerabilities and create opportunities for privacy and data breaches. Hence, another category of solutions identified focused on addressing cybersecurity concerns (such as data authentication and data cloning) inherent to these technologies that can be exploited by criminals and hackers. In this sense, certain types of technology merely serve to counteract new risks that emerging technology introduce, a critical factor when dealing with the profitable and criminal nature of this activity.

5. Expert opinion

The global market for anticounterfeiting solutions is projected to mature into a $35 billion dollar industry [18]. Reflecting this increased attention and investment, over the past 7 years, the landscape for fake medicines technologies has significantly increased, with more than 40 unique technologies being commercialized and over half of them now available for use [45]. While this is encouraging, governments, regulators and pharmaceutical companies continue to struggle with how to utilize forms of traditional and digital anticounterfeiting technologies that are being

developed, while also determining how they best fit with their individual pharmaceutical product offerings, diverse markets, geography, and unique supply chain vulnerabilities. Fortunately, the international legal, policy, and regulatory environment needed to mobilize stakeholder rhetoric into action may be taking shape. This includes renewed efforts in global governance to fight fake medicines including regional treaty instruments such as the Council of Europe's MEDICRIME Convention that entered into force in 2016, the Council of European Union's Falsified Medicines Directive, domestic laws such as the United States' 2013 Drug Supply Chain Security Act, and other national and local laws and decrees [5,16,58,84,142,143]. This emerging global drug-safety policy environment could act as a catalyst for the translation of the digital technologies we have identified into real-world solutions, tools we argue are critical in addressing a drug supply chain that continues to become more globalized, digital, and a lucrative target for criminals engaged in the international trade in fake medicines.

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