Medicine quality in high-income countries: The obstacles to comparative prevalence studies

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Abstract
The entry of falsified and substandard medicines into the legitimate pharmaceutical supply chain has negative impacts on healthcare systems, patient safety, and patient access to medicine. The COVID-19 pandemic has highlighted the importance of access to safe medicine through legitimate pharmaceutical supply chains and the willingness of criminals to target medical products such as PPE (personal protective equipment) and COVID-19 treatments. In this article, we analyse data from the United Kingdom (UK) national medicine alert and recall database to identify and understand recent cases of substandard and falsified medicine in the UK’s healthcare systems. Using the UK as a case study, we describe that national drug alert and recall data are useful in their current form to record and understand cases of substandard and falsified medicines in the supply chain. However, if regulatory agencies published further data, these drug recall databases may be useful to support longitudinal and international comparative medicine quality studies. We suggest that regulatory agencies publish the number of affected medicine packs in each recalled batch, as part of the recall process. This will help policy makers, practitioners, and researchers to better understand, monitor and compare the quality of medicines within legitimate supply chains.

Keywords
Medicine quality, substandard medicine, falsified medicine, supply chain, product recall, pharmaceutical industry, comparative healthcare

Date received: 6 April 2021; accepted: 23 September 2021

Introduction
The issue of Substandard and Falsified medicines (SF Medicines) affects high-income and low- and middle-income countries.1 Substandard medicines are authorised medical products which are ‘out of specification’ and fail to meet either their quality standards or specifications, or both. Falsified medicines are ‘medical products that deliberately/fraudulently misrepresent their identity, composition or source’.2 Within the medicine quality context, these terms are increasingly replacing the term counterfeit, which is more closely aligned with copyright and intellectual property infringements.3 The term falsified medicine is preferred by the European Commission and the Medicines and Healthcare

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products Regulatory Agency (MHRA). One might expect that high-income countries with established medicine regulatory bodies have lower rates of SF Medicines in their legitimate supply chains, and higher standards of medicine quality compared to lower income countries. However, we cannot be sure how medicine quality changes over time, nationally or internationally. In this article, we use the (United Kingdom) UK medicine alert and recall database as a case study to discuss the opportunities and challenges of comparative and longitudinal medicine quality studies in high-income countries.

**Empirical examples of SF Medicine in high-income countries**

SF Medicines have been linked to thousands of deaths internationally. Furthermore, SF Medicines have an enormous economic impact, which is estimated at between US$10 billion and US$200 billion annually worldwide. Moreover, SF Medicines negatively impact global access to essential medicines and adversely impact antimicrobial resistance. In the high-income country context, a falsified version of Bevacizumab (Avastin®), an anticancer medicine, was found in the legitimate supply chain. This medicine, which is usually manufactured by Roche, and contained starch and salt instead of containing the active pharmaceutical ingredient (API). Recently, there has been a case of falsified Iclusig® (Ponatinib) identified in Switzerland and circulated in Europe and the Americas which contained paracetamol instead of Ponatinib. This medicine was circulated through the legitimate supply chain, via pharmaceutical wholesalers. Even more recently, due to the COVID-19 pandemic, there have been numerous cases of falsified COVID treating medical products circulating across the globe. More broadly, the Pharmaceutical Security Institute (PSI) publishes annual figures concerning counterfeiting, illegal diversion and theft incidents; they too have identified that illegal medicine activity is an increasing problem. From 2015 to 2019, the PSI described an increase in incidence of 69% and the PSI estimated that high-income countries are affected by 20% of all globally circulating SF Medicines. This lack of data inhibits our understanding of the extent of medicine quality issues in the high income context and restricts our ability to identify and compare good manufacturing and distribution practice on an organisational and national level.

**Existing policy and innovative solutions**

In order to reduce the incidence of medicine falsification and streamline the recall of substandard medicine, international governments in high-income countries have introduced and implemented innovative medicine serialization and traceability regulations. These regulations require pharmaceutical companies to serialise medicine packs and mandate that supply chain partners track and trace or authenticate medicines as they pass through the legitimate supply chain. The US approach is called the US Drug Supply Chain Security Act (DSCSA), and the European Union (EU) approach is called the EU Falsified Medicines Directive (EU FMD). The EU FMD requires pharmacists to decommission medicines as they are dispensed to patients, and requires hospitals, community pharmacies and wholesalers to implement software and hardware systems to facilitate medicine authentication. At the point of scanning, this software alerts the user via pop-up messages regarding the medicine’s status, for example, expired, recalled or potentially falsified, an approach which is already having an impact on pharmacy and general practice. However, these extensive policies and regulations are not the
absolute solution to address poor-quality medicine. In high-income countries, regulations such as the EU FMD have been contested due to a lack of reliable prevalence data, which describe the extent of SF Medicine in high-income countries. There is a perception that falsified medicines are not a prevalent problem in high-income countries when compared to the operational and financial impact of these regulations.\textsuperscript{37-40} Many healthcare professionals in high-income countries have questioned whether an approach, such as the FMD, is proportionate to the problem.\textsuperscript{41} To encourage the adoption of these regulations in high-income countries, we should first estimate and communicate the extent of the SF Medicine problem in the legitimate supply chain.

**Illustrative case study**

The aims of this case study are achieved by analysing data collected from an 8-year period (2012–2020) and discussing national medicine quality. A search of the UK MHRA website data\textsuperscript{20} and MHRA archives was conducted. The first search assessed drug alerts and recalls for defective medicines issued by the MHRA, and the second search investigated company-led recalls. Data searches between 1 January 2012 and 1 January 2020 were performed. Company-led recalls occur when defective medicines with a ‘limited and known’ distribution, leave the manufacturing site and are recalled by the manufacturing company before they are completely distributed into the supply chain, and therefore do not require widespread communication.\textsuperscript{42} As company-led recalls on the MHRA’s website do not backdate to January 2012, the MHRA archives were also searched. The date of the alert, name of the medicine, type of the defect, dosage form, number of affected batches, class of drug alert and recall level were recorded. An exclusion criterion was applied in Figure 1, according to the Almuzaini et al.\textsuperscript{42} methodology. Drug alerts and recalls issued by the MHRA are graded into four different classes (1–4) according to the level of risk they pose to public health. Class 1 relates to life-threatening defects and requires an urgent recall. Class 2 medicines relate to harmful defects, which require a

![Flow diagram of MHRA's website and archive search strategy, and the number of drug alerts and company-led recalls between 1 January 2012 and 1 January 2020.](image-url)
recall within 48 h; although the defect can be harmful to the patient, the effect is not life-threatening.2 Class 3 alerts are not necessarily issued for the safety of the patients and require attention within 5 days; these alerts are often concerning issues associated with marketing authorisation.2 Class 4 alerts are ‘caution in use’ notices which do not pose a serious threat to the patients and are only there to provide advice.2 Two types of defective medicines were identified in these drug alerts, recalls and risk communication documents issued by the MHRA; these were substandard (licensed and unlicensed/unregistered) and falsified medicines. The MHRA decided which products were falsified. The UK dataset was chosen as the example context as recalled data were freely available, and it is one of the top 10 biggest global pharmaceutical markets in the world.23

Using the UK as a case study, this article describes the number of falsified and legitimate but poorly manufactured or distributed medicines recalled in the UK from the legitimate supply chain in recent years. Between 2012 and 2020, there were 210 drug alerts and recalls (Figure 1; 136 MHRA alerts/recalls and 74 company-led alerts/recalls). The mean annual number of MHRA recalls was 17 during this same period. Between 2012 and 2020, there were 342 different medicines recalled as part of these 210 recalls. This includes 233 individual medicines recalled by the MHRA and 109 medicines recalled from pharmaceutical companies. The majority (n = 325) of the defective medicines identified in this period were substandard and 17 were falsified. The mean annual number of medicines recalled by the MHRA for the period 2012–2020 was 29 (Figure 1).22

There were five cases of Class 1 drug recalls and alerts, which are the most serious cases according to the level of risk they pose to public health (Table 1). The other alerts and recalls were often due to contamination, and device or packaging defects (Table 2).

The most common reason for substandard medicine recall was contamination, which demonstrated an annual mean of 13 recalled products per year (2012–2020). Delivery defects also contributed significantly to medicine recalls during this period. Between 2012 and 2020, 3 falsified medicine recall alerts and 17 individual falsified medicines (annual mean of 2 per year) were reported by the MHRA (Table 3).

### Medicine alerts, recalls and national medicine quality

When known SF Medicines make their way into the legitimate supply chain in high-income countries, these cases are reported to wholesalers, healthcare practitioners and the public in an effort to alert and sometimes remove these products from the supply chain. The data concerning these alerts and recalls are often stored on open access databases. This approach is adopted by many high-income countries, including Australia, Canada, Germany, New Zealand, Ireland, the UK and the United States. The data presented in this article describes the number of recalls from the UK drug recall database from 2012 to 2020. In an attempt to use these data as a proxy or surrogate marker for national medicine quality in the legitimate supply chain, some challenges were faced. This case study has identified that the mean annual number of MHRA recalls and alerts in the UK over the past 8 years is 17 (2012–2020), which equates to an annual mean of 29 individual products per year (2012–2020), including a total of five cases of Class 1 medicine recalls, and an average of two falsified medicines per year. It would be useful to compare these data with other periods of time in the United Kingdom to understand whether the problem is changing. It would also be useful to compare these data with other countries to understand how the United Kingdom’s medicine quality standard compares internationally. From here, we could establish

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**Table 1.** A description of Class 1 recalls reported by the MHRA from 2012 to 2020.

| Date       | Type of defect | Medicines | Formulation                          | Defect description                                      |
|------------|----------------|-----------|--------------------------------------|----------------------------------------------------------|
| 5 July 2018| Contamination  | Valsartan 40, 80, 160 mg Capsules, hard | Possible contamination with an impurity NDMA which has genotoxic and carcinogenic potential |
|           |                | Valsartan 40, 80, 160, 320 mg Film-coated tablets |                                                          |
|           |                | Valsartan/Hydrochlorothiazide 160/12.5 mg Tablets |                                                          |
| 4 June 2014| Contamination  | Lipid Phase Parenteral Nutrition Total parenteral nutrition | Due to a potential contamination with Bacillus cereus identified following a small number of reported cases of Bacillus cereus septicaemia affecting neonates |
| 18 June 2013| Contamination  | Amphotericin 50 mg powder for solution for infusion | Lack of sterility assurance |

MHRA: Medicines and Healthcare products Regulatory Agency; NDMA: N-nitroso-dimethylamine.
whether other countries or manufacturers manage the issue of medicine quality in a more effective way and learn from their practice. If we could identify that there had been a change in medicine quality we could investigate through qualitative and quantitative research, why this was the case. From these data, we could perform further qualitative research to better understand the influence of changes in the regulatory authority strategy, or pharmaceutical company management and governance on medicine quality. It is clear, in the UK, that substandard medicines are a more common problem than falsified medicines in the legitimate supply chain. What is not clear is whether the problem is changing or how the problem compares with other nations.

Ideally, the prevalence of poor-quality medicine (substandard and falsified) could be calculated by dividing the number of medicines recalled (the numerator) by the number of medicines used within the country (denominator). The number of medicine packs used in any given country is often available, for example, the national health service (NHS) business service authority provides prescription data which are freely available to the public. However, freely available recall data typically include the product name, a description of the recall and the affected batch numbers, but does not contain data concerning how large the batch was or the number of affected packs. It also does not state what proportion of a batch went to the reporting country. Considering these points, we believe that there is currently no accurate available numerator to estimate the prevalence of poor quality medicine in a high-income country. Therefore, we call on medicine regulators to publish the total number of affected packs in each batch, delivered to each country, when recalling medicinal products from the market. This will help policy makers, practitioners and researchers to explore, estimate, monitor and compare the prevalence of poor-quality medicine in international legitimate supply chains. It may also help to inform and support future research, as well as policy and management work in the area of medicine quality in the legitimate pharmaceutical supply chain.

Table 2. A summary of defect details of all the company-led recalls and MHRA drug alerts (2012–2020; excluding falsified medicines).

| Defect type                          | Number of medicines affected (2012–2020) | Defect details                                      | Number of medicines affected (2012–2020) |
|-------------------------------------|-----------------------------------------|----------------------------------------------------|-----------------------------------------|
| Contamination                       | 101 (31%)                               | Impurities                                         | 85 (26%)                                |
|                                     |                                         | Lack of sterility assurance                        | 8 (2%)                                  |
|                                     |                                         | Microbial contamination                             | 8 (2%)                                  |
| Delivery defect (e.g. quality defect with the medicine delivery device) | 50 (15%)                               | Damage, leakage or loose seal                       | 19 (6%)                                 |
|                                     |                                         | Fault with device                                   | 29 (9%)                                 |
|                                     |                                         | Others                                              | 2 (1%)                                  |
| Major packaging defect              | 18 (6%)                                 | Missing or incorrect name, strength or active ingredient of medicine on carton or box | 14 (4%)                                 |
|                                     |                                         | Packing medicine in the wrong carton                | 4 (1%)                                  |
| Minor packaging defect              | 33 (10%)                                | Error on PIL                                        | 9 (3%)                                  |
|                                     |                                         | Incorrect administration instructions                | 3 (1%)                                  |
|                                     |                                         | Others                                              | 21 (7%)                                 |
| Stability failure                   | 23 (7%)                                 | Unspecified stability failures                      | 15 (5%)                                 |
|                                     |                                         | Stability failure of active ingredient or dissolution prior to expiry | 8 (3%)                                 |
| Potency                             | 5 (2%)                                  | Reduced potency of active ingredient                | 3 (1%)                                  |
|                                     |                                         | Others                                              | 2 (1%)                                  |
| Defect in active ingredient         | 19 (6%)                                 | Active ingredient out of specification (either more or less) or defect inhomogeneity | 19 (6%)                                 |
| Other defects                       | 76 (23%)                                | Others including GMP deficiencies at manufacturing site | 76 (23%)                                |
| Total                               | 325 (100%)                              |                                                     | 325 (100%)                              |

MHRA: Medicines and Healthcare products Regulatory Agency; PIL: Patient Information Leaflet; GMP: Good Manufacturing Practice.
Limitations

Regarding substandard medicine, this study considers only legitimately manufactured medicines and defects at manufacture and distribution. This study does not consider medicines which have become substandard after manufacture and distribution due to inappropriate storage conditions within a healthcare facility. Concerning falsified medicine, this study considers falsified medicines identified in the legitimate supply chain and does not aim to estimate the total number of falsified medicines in circulation in the UK in illegitimate supply chains.

Conclusion

Substandard medicine recalls are a more common issue in the UK legitimate pharmaceutical supply chain than falsified medicine recalls. It is important to explore, estimate, monitor and compare drug recall data to understand

Table 3. Drug alerts relating to falsified medicine.

| Year of alert | Brand name of medicine (generic product name) | Class of drug alert for MHRA recalls (1–4) | Formulation | Recall level | Defect description |
|---------------|-----------------------------------------------|---------------------------------------------|-------------|-------------|--------------------|
| 2014          | Herceptin 150 mg (Tratztuzumab)                 | Not applicable                              | Powder for concentrate for solution for infusion | Wholesaler level | A small number of vials labelled as Italian Herceptin 150 mg are suspected of being falsified |
| 2019 (June)   | Clexane 8000 IU 0.8 mL 1 × 10 (Enoxaparin sodium) | 2                                           | Subcutaneous injection Gel | Pharmacy level | Medicines have been taken out of the regulated medicines’ supply chain during distribution and later reintroduced44 |
|               | Dovobet gel 1 × 30g (Betamethasone dipropionate calcipotriol monohydrate) |                                             | Powder for inhalation | Tablets |                                   |
|               | Incrise inhaler 55 mcg 1 × 30 doses (Umclidinium bromide) |                                             | Inhaler |               |                                   |
|               | Neupro 4 mg/24 h 1 × 28 patches (Rotigotine)    |                                             | Transdermal patches | Tablets |                                   |
|               | Provisacor (sold as Crestor) 10 mg Tabs 1 × 28 (Rosuvastatin) |                                             | Inhaler |               |                                   |
|               | Seebr Breezhaler 44 mg 1 × 30 doses (Glycopyronium bromide) |                                             | Powder for inhalation | Tablets |                                   |
|               | Spiriva Inhalation Powder 18 mcg Cap 1 × 30 (Tiotropium bromide) |                                             | Inhaler |               |                                   |
|               | Vimpat 100 mg Tabs 1 × 56 (Locosamide)         |                                             | Gel | Pharmacy level | Medicines have been taken out of the regulated medicines’ supply chain during distribution and later reintroduced |
| 2019 (July)   | Dovobet gel 2 × 30 (as above)                  | 2                                           | Gel | Pharmacy level |                                   |
|               | Incrise Ellipta 55 mcg inhaler 1 × 30 doses (Kosei Pharma UK Ltd) (as above) |                                             | Inhaler |               |                                   |
|               | Neupro 4 mg/24-h transdermal patch 1 × 28 (as above) |                                             | Transdermal patch | Patient level |                                   |
|               | Seretide Evohaler 250 mcg 1 × 120 (Fluticasone/Salmeterol) |                                             | Inhaler | Pharmacy level |                                   |
|               | Spiriva 18 mcg inhaler powder capsules 1 × 30 (as above) |                                             | Powder for inhalation | Tablet | Patient level |
|               | Vimpat 100 mg tablet 1 × 56 (as above)         |                                             | Inhaler | Pharmacy level |                                   |
|               | Duroresp Spiromax 160/4.5 mcg (budesonide formoterol fumarate dihydrate) |                                             | Inhaler |               |                                   |
|               | Incrise Ellipta 55 mcg inhaler 1 × 30 (MPT Pharma Ltd) (as above) |                                             | Gel | Pharmacy level |                                   |

MHRA: Medicines and Healthcare products Regulatory Agency.
whether the overall manufacturing and distribution of SF Medicines is changing in high-income countries. However, freely available drug alert and recall data in its current form are not a reliable estimate measure of medicine quality due to the lack of a suitable numerator. We propose data sharing to facilitate comparative medicine quality studies in legitimate pharmaceutical supply chains. We call on policy makers and regulators to work with pharmaceutical companies to publish the total number of affected medicine packs in each batch, entering each individual country when publishing drug alert and recall data.

**Declaration of conflicting interests**

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Oxford University Hospitals NHS Foundation Trust has supported Dr Naughton’s time in preparing this manuscript.

**Ethics and consent statement**

This article conveys the opinions of the authors. Neither approval nor informed consent is required.

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