Impact of Drug Recalls on Patients in The Netherlands: A 5-Year Retrospective Data Analysis

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Drug recalls occur frequently and have the potential to impact considerable numbers of patients and healthcare providers. However, in the absence of a comprehensive overview the extent of conducted recalls and their impact on patients remains unknown. To address this, we developed a comprehensive overview of drug recalls affecting patients. We compiled this overview based on the drug recall registrations from the Jeroen Bosch Hospital (JBZ), the University Medical Center Utrecht (UMCU), and the Royal Dutch Pharmacists Association (KNMP). A retrospective data analysis was conducted to identify drug recalls that affected patients. Specifically, we defined these as drug recalls that required patients to actively switch their drug to a different batch or brand of the same drug or to switch to a drug within the same or a different class of drugs. To quantify the impact, we used real-world drug dispensing data. Between January 1, 2017, and December 31, 2021, we identified 48 drug recalls that necessitated patients to make active changes to their medications an estimated 855,000 times. Most of the affected patients (292,000) were required to switch to a different brand of the same drug, whereas in 95,000 cases patients had to switch to a drug from another drug class. Our study suggests that a significant number of patients are affected by drug recalls. Future efforts are needed to elucidate patients' experiences and preferences regarding drug recalls, which could provide valuable insights to aid decision-making by relevant (national) authorities concerning drug recalls.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Currently, little information exists regarding the extent of drug recalls and their impact on patients. To date, no prior research has been conducted to determine the extent to which patients are affected by drug recalls.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ The objective of this study was to develop a comprehensive overview of drug recalls impacting patients in the Netherlands and to assess their subsequent implications on the patient population.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Our study suggests that a large number of patients are forced to switch drugs as a result of drug recalls, as evidenced by a representative overview relying on data from three recall registration databases.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Given the significant number of patients affected by drug recalls, future efforts are needed to identify how patients experience a drug recall and to ascertain patient preferences regarding drug recalls. These efforts could provide valuable insights to aid decision making by relevant (national) authorities concerning drug recalls.

In recent years, the number of drug recalls with the potential to impact large numbers of patients and healthcare providers has increased. Since 2018, worldwide many drug recalls were issued because of nitrosamine impurities, e.g., in angiotensin II receptor blockers (ARBs), such as valsartan and losartan.[1–3] A large number of patients had to switch their drugs as a result of these drug recalls.[4,5] Following this, additional drugs were found to be contaminated with nitrosamines and were recalled.[6] Also other reasons for drug recalls have been reported, such as the malfunction of an adrenaline autoinjector pen, inhalers failing to administer the complete designated dose, or the withdrawal of a drug's registration.[7–9]

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The recall of drugs is a key instrument employed by drug regulators responsible for human drug products to prevent patient exposure to a defective or potentially harmful drug.[10,11] Marketing authorization holders (MAHs) are mandated to report any (suspected) product quality defect. In the European Union (EU), the European Medicines Agency (EMA) coordinates the assessment of centrally authorized drug products, while relevant national regulatory authorities are responsible for assessing nationally authorized products. One aspect of the assessment process involves determining the appropriate classification of a drug recall. This classification, which is based on the associated risk of the product quality defect, serves to determine whether a drug recall will be implemented at the level of distributors, pharmacies, or patients.[12]

The communication and implementation of drug recalls have the potential to significantly impact patient confidence in drugs. Effective communication of drug recalls could improve patient confidence by demonstrating effective prevention of exposure to potentially hazardous drug defects. However, the communication and implications of drug recalls could also result in decreased patient confidence in drugs, leading to decreased medication adherence.[13] In instances where a patient-level drug recall is deemed necessary, patients are requested to actively return their home supply of drugs to the pharmacy. In exchange, patients are provided with either a different batch of the same drug, a different label of the same drug, or an alternative drug. When a drug recall is implemented at the level of pharmacies or distributors, the recalled product is exclusively withdrawn from pharmacies and/or distributors without direct notification to the patient. Nonetheless, patients may still be affected due to possible drug shortages resulting from such recalls. Additionally, the recall of drugs can impact patient–healthcare provider relationships and patient trust in the healthcare system and governmental entities, potentially leading to both positive and negative outcomes.[14]

Currently, little information is available on the scope of drug recalls and how many patients are affected by drug recalls. Therefore, we undertook this study to create an overview of drug recalls that affected patients in the Netherlands and to establish the impact on patients.

METHODS

Recall overview

In order to obtain a comprehensive overview of drug recalls, we contacted regulatory agencies and professional associations. We reached out to the Dutch Health and Youth Care Inspectorate (IGJ), the Dutch Medicines Evaluation Board (MEB), and the European Medicines Agency (EMA) — organizations that are involved in assessing and advising on drug recalls. Furthermore, we contacted the Royal Dutch Pharmacists Association (KNMP), the Dutch Generic and Biosimilar Medicines Association (BOGIN), and the Dutch Association Innovative Medicines (VIG).

None of the regulatory agencies or manufacturer associations could provide a readily accessible complete overview of drug recalls. Therefore, we developed an overview of drug recalls communicated from 2017 until 2021 based on the drug recall registrations and associated drug recall letters from a Dutch top clinical hospital (Jeroen Bosch Hospital (JBZ)), a Dutch university medical center (University Medical Centre Utrecht (UMCU)), and the KNMP. We merged the drug recall registries and removed any duplicates. Drug recalls of registered drugs or their administration devices, communicated from January 2017 to December 2021, were considered for inclusion in the present overview. Entries in the recall databases that were not related to registered drugs or did not pertain to the recall of a drug were excluded. Furthermore, we excluded drug recalls relating to the preparation of ready-for-administration drugs. Ready-for-administration drugs are mostly intravenous (i.v.) drugs prepared in small-scale batches within a hospital pharmacy and are subsequently distributed to designated hospital wards. The implications of these recalls are limited to minor drug quantities, with patient involvement being absent, and administration of drugs to patients remains unaffected, since alternative batches of ready-for-administration drugs are available. We then excluded drug recalls that did not fall within our definition of recalls affecting patients and cases where available data were insufficient.

Data collection

For each drug recall, we collected the following variables: product name(s), recall date, registration number(s), level of a drug recall (patient, pharmacy or wholesaler), product defect description, likelihood of expected shortage, and availability of alternative product(s). We categorized the product defects as: manufacturing laboratory controls issue (e.g., a deficit in process controls); product contamination and sterility issues; product label issues; product packaging issues; product physical issues, e.g., product coating cracked; or suspension of the drug's registration.[15]

Definition of drug recalls affecting patients

We defined drug recalls affecting patients as drug recalls that required patients to actively switch their drug to a different batch or brand of the same drug or to switch to a drug within the same or a different class of drugs. This definition includes both patient-level recalls as well as non-patient-level recalls. To assess whether a drug recall affected patients, we used the information in the drug recall letters regarding the level of the drug recall, the recommended actions following a drug recall, the likelihood of drug shortages, and the availability of alternative drug products. For example, a non-patient-level drug recall that resulted in a drug shortage subsequently forcing patients to switch their drugs was considered to affect patients.

We verified whether the drug recalls affecting patients were registered in all three of the recall registrations databases to ensure the validity of the data contained in our overview. Additionally, we analyzed recalls that were present in only one or two databases to identify any potential explanations for their absence in the remaining databases.

Drug dispensing data

We utilized real-world drug dispensing data from the Dutch Foundation for Pharmaceutical Statistics (SFK) to determine the number of patients impacted by a drug recall. SFK acquires drug dispensing data from community and outpatient pharmacies throughout the Netherlands, rendering the data applicable to patients within the community setting. We defined active drug users as patients who had received a drug within the 4 months preceding the announcement of a drug recall. In general, patients in the Netherlands receive their chronic drugs every 3 months. To ensure reliable drug dispensing data, we collected drug dispensing data starting from the first day of the month in which the drug recall was announced, up to 4 months prior to that date. For example, for a drug recall announced on May 15, we collected drug dispensing data from January 1 until May 1. To prevent the inclusion of the same patient in one drug recall more than once, we counted individuals who were using two or more drugs impacted by the same recall as a single case. Several drug recalls were carried out simultaneously, pertaining to the same drug type, with identical product defects, and affecting the same group of patients. In these cases, we combined drug dispensing data from these identical drug recalls and

presented active drug users per patient population affected by (a series of) drug recalls.

To arrive at the total number of times patients had to switch their drugs, we added up all the active drug users per patient population. These patients may not necessarily be unique patients, as for example, patients affected by an ARB recall may also be affected by a drug recall involving a biguanide.

Ethics and confidentiality

Because our research exclusively used database research without involving human subjects, obtaining institutional review board approval was deemed unnecessary for this study. In order to protect the confidentiality of market-sensitive data pertaining to the user count of drugs from specific manufacturers, we only report on the generic name of recalled drugs.

RESULTS

Between January 1, 2017, and December 31, 2021, a total of 161 entries in the drug recall registration databases were detected, of which 92 were registered by the JBZ, 111 by the UMCU, and 58 by the KNMP. We removed duplicate entries ($n = 100$) and excluded entries unrelated to registered drugs ($n = 18$) or, upon further investigation, were found not to be a drug recall ($n = 21$). For instance, one of the drug recall registrations also contained entries concerning the recall of blood drug test results. Twelve drug recalls related to small batches of ready-to-administer drugs were excluded. We further excluded 54 recalls that did not directly affect patients. For eight drug recalls, insufficient data were available for assessment. Finally, we identified 48 drug recalls as directly affecting patients (Figure 1).

Out of the 48 drug recalls that we evaluated to affect patients, 36 recalls (75%) were consistently recorded in all three drug recall databases (Figure 2). Eight recalls (17%) were registered in two of the three databases. Additionally, four recalls (8%) were registered in only one of three databases.

Over a five-year period, patients switched their drugs an estimated 855,000 times due to drug recalls. The impact of these drug recalls on patients between 2017 and 2021 is visually depicted in Figure 3. As several recalls affected the same patient population during the same time period, these recalls were consolidated into one population of affected patients (Figure 1). Specifically, we combined the active drug users of the following drug recalls into a single population of affected patients: six recalls of ARBs with or without diuretics (July and August 2018); three recalls relating to ARBs with or without diuretics (December 2018); two recalls of ARBs with or without diuretics (March 2019); two recalls of H2 receptor antagonists (October 2019); three recalls of biguanides (November 2020); two recalls of ARBs with or without diuretics or calcium channel blockers or neprilysin inhibitors (July 2021); and two recalls of drugs used in nicotine dependence (September and October 2021). This resulted in 35 individual patient populations impacted by drug recalls. Among the 35 affected patient

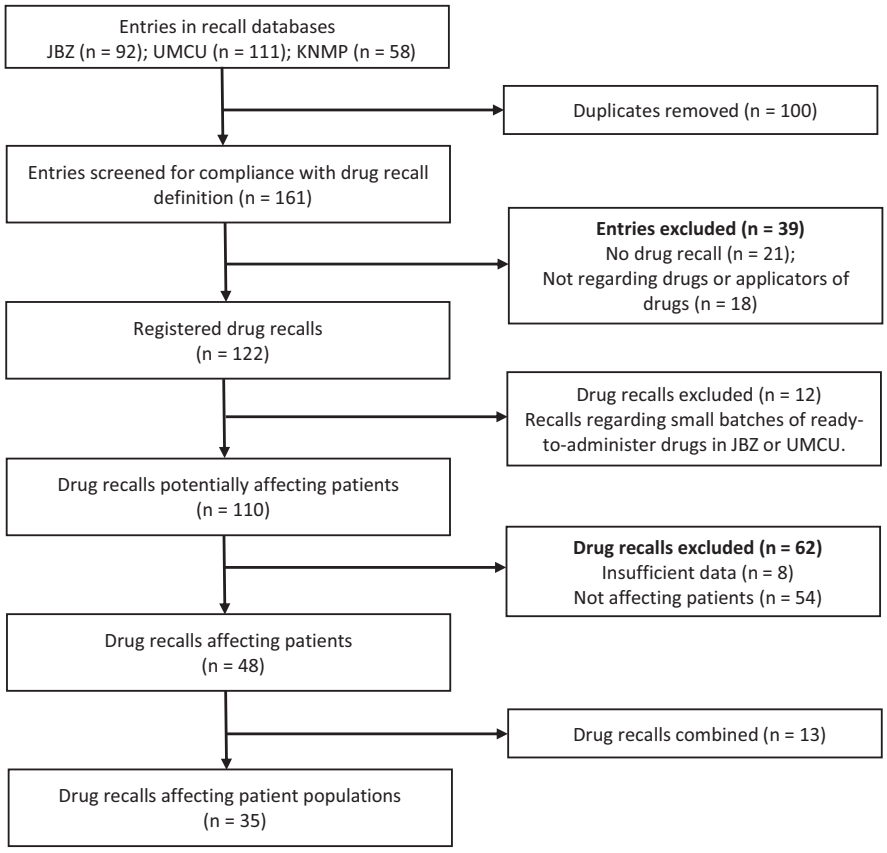

Figure 1 Flowchart that visualizes the exclusion steps for the drug recall entries. JBZ, Jeroen Bosch Hospital; KNMP, Royal Dutch Pharmacists Association; UMCU, University Medical Center Utrecht.

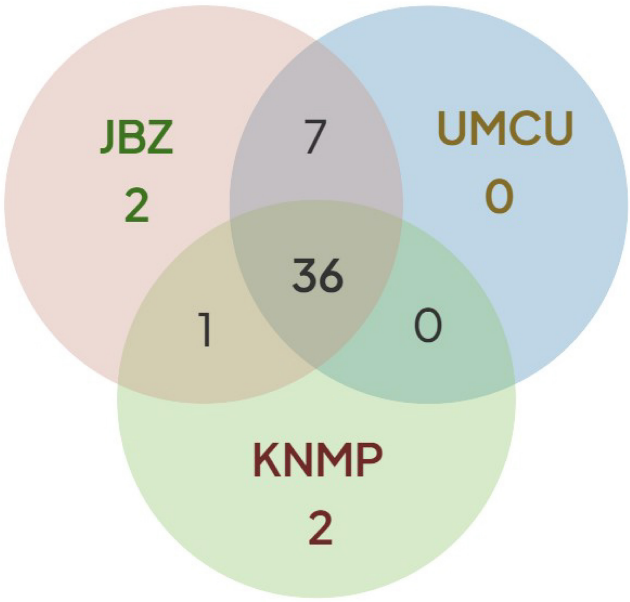

Figure 2 Venn diagram indicating in which drug recall registration database the drug recalls affecting patients were registered. JBZ, Jeroen Bosch Hospital; KNMP, Royal Dutch Pharmacists Association; UMCU, University Medical Center Utrecht.

populations, 6 encompassed more than 80,000 patients, while 17 consisted of fewer than 1,000 affected patients.

The primary factors contributing to drug recalls that had the most significant impact on patients were attributed to product contamination and sterility issues, affecting patients a total of 630,000 times across 12 out of 35 patient populations, as depicted in **Figure 4**. Moreover, drug recalls stemming from product physical issues affected patients 177,000 times across 7 out of 35 patient populations, whereas drug recalls resulting from manufacturing laboratory controls issues impacted patients 28,000 times across 3 out of 35 patient populations. Three drugs were recalled because the registration of the drug was suspended, and we classified these recalls accordingly.

As a consequence of drug recalls, patients from 6 out of the 35 patient populations switched to a drug from a different drug class 95,000 times, as indicated in **Figure 5**. A switch to a different drug within the same drug class was required 271,000 times for patients across 5 out of the 35 patient populations. Additionally, patients from 13 out of the 35 patient populations changed to an alternative brand of the same drug ~ 292,000 times. Lastly, 197,000 times patients across 11 out of the 35 patient populations switched to a different batch of the same drug.

DISCUSSION

Over the period spanning from 2017 to 2021 a total of 48 drug recalls directly affected 35 patient populations, requiring patients to switch to alternative drugs for an estimated total of 855,000 times. Among these recalls, those triggered by concerns of product contamination and sterility had the most substantial impact, affecting patients 630,000 times. Notably, most of the time (292,000) patients had to switch to a different brand of the same drug, while in 95,000 cases patients were required to switch to an entirely different drug class.

The established impact of drug recalls on patients in this study was limited to the impact on active drug users that had to switch drugs. In reality the number of patients affected by a drug recall is substantially larger, since the communication of a drug recall can already impact patients and influences, for example, the patient's confidence in drugs and may have impact on medication adherence. In addition, some drug recalls created a lot of attention in the media (worldwide), resulting in a substantial number of patients reaching out to their healthcare providers.[16,17] This concerns also patients who were not affected by the specific recall.

Our study uncovered a notable limitation in the availability of a comprehensive overview of drug recalls, which posed challenges in accurately assessing the impact of these recalls on patients over the specified period. Moreover, on the one hand, we identified a number of limitations that may have contributed to an underestimation of the number of patients affected. First, we constructed a comprehensive compilation of drug recalls within the Netherlands by sourcing drug recall registrations from two distinct hospital pharmacies (one peripheral and one academic) along with data from the Dutch professional association of pharmacists. The discrepancies that we found between the three drug recall registrations of drug recalls affecting patients could be explained by the drug type or the fact that this drug was not in use in the relevant hospital. While we have confidence in the reasonable accuracy of our complied overview, we acknowledge the potential omission of certain recalled drugs from the period between 2017 and 2021 in the Netherlands. As such, this overview might represent a conservative estimation of the actual occurrences. Second, the calculated number of affected patients through our search using SFK data underestimates the actual number of affected patients. SFK solely receives drug dispensing data from community and outpatient pharmacies in the Netherlands, thus patients receiving care in hospitals or long-term care facilities (such as nursing homes or mental health institutions) are not included. Additionally, our inclusion of drug dispensing data spanning a 4-month window prior to a drug recall assumes the comprehensive incorporation of all active drug users. Nonetheless, it is plausible that certain active drug users might possess an ample supply of drugs at home, negating the necessity for prescription refills within this stipulated 4-month time frame. However, we posit that this scenario would apply to a minor patient subset, as the conventional practice involves patients acquiring their drugs every 3 months. Third, our analysis excluded drug recalls that lacked a documented impact or had unknown implications on potential shortages and subsequent forced switches. Consequently, recalls that may have indeed affected patients through drug shortages but lacked identifiable documentation were inadvertently omitted.

On the other hand, we also identified several limitations that could have contributed to an overestimation of patients that were forced to actively switch drugs. First, the summation of active drug users to arrive at a total of 855,000 times patients were affected may have led to an overestimation of unique patients. A patient affected by an ARB recall, for example, could also be affected by a drug recall

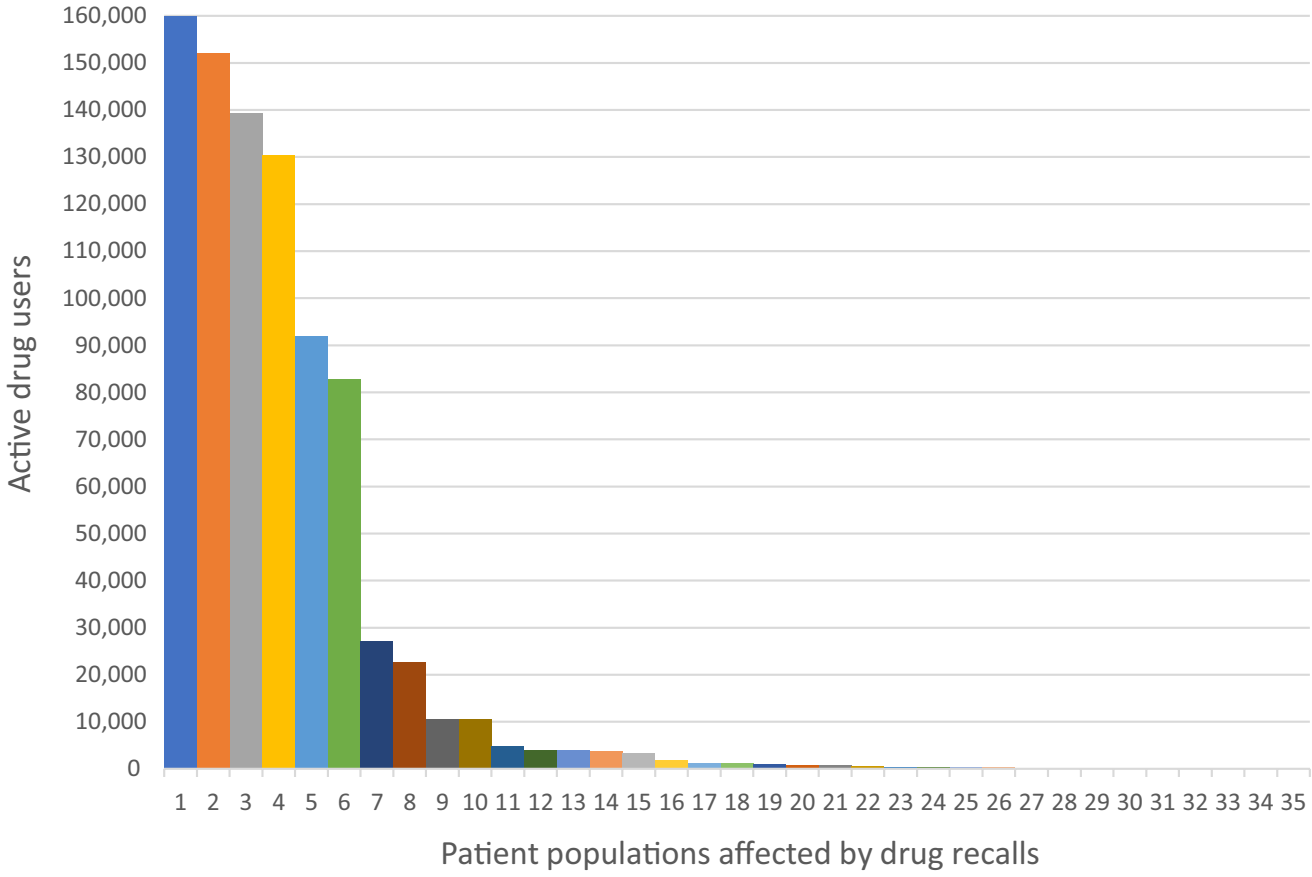

Figure 3 Overview of patient populations affected by drug recalls and the associated active drug users that were necessitated to make active changes to their medications. Drug recalls are only reported by their generic name in order to protect the confidentiality of market-sensitive data pertaining to the user count of drugs from specific manufacturers. 1, selective (inhalation) beta-2 adrenoceptor agonist; 2, angiotensin II receptor blocker with or without diuretics; 3, biguanide; 4, angiotensin II receptor blocker with or without diuretics/calcium channel blockers/neprilysin inhibitors; 5, angiotensin II receptor blocker with or without diuretics; 6, H2 receptor antagonist; 7, topical corticosteroid; 8, angiotensin II receptor blocker with or without diuretics; 9, epinephrine auto-injector; 10, drugs used in nicotine dependence; 11, benzodiazepine; 12, epinephrine auto-injector; 13, analgesic and antipyretic; 14, ophthalmic fluoroquinolone; 15, proton pump inhibitor; 16, fibrate; 17, topical antineoplastic; 18, reusable insulin pen injector; 19, mucolytic; 20, reusable somatropin pen injector; 21, vasopressin analog; 22, progesterone receptor modulator; 23, epinephrine auto-injector; 24, low-molecular-weight heparin; 25, oral osmotic laxative; 26, topical antiseptic; 27, antiepileptic; 28, oral anticholinergic; 29, JAK inhibitor; 30, opioid nasal spray; 31, interleukin inhibitor; 32, opioid nasal spray; 33, injectable antipsychotic; 34, ophthalmic corticosteroid; 35, injectable cephalosporin.

involving a biguanide. However, we contend that despite being the same individual, the patient experienced the consequences of both drug recalls. Second, in most drug recalls only specific batches were identified as defective, meaning that only patients possessing these particular defective batches were required to return their drug supplies, rather than all drug users. However, since batch numbers were absent in the drug dispensing data from SFK, it was not feasible to identify affected patients based on the recalled drug's batch. This may have led to an overestimation of patients that had to switch drugs. On the contrary, however, pharmacists do not always know which batch has been distributed to a patient, and therefore resort to informing all patients who have received the drug, prompting them to ascertain if their supply corresponds to the recalled batch. Third, when certain drug recalls exclusively affected specific batches and potential shortages were anticipated, not all patients experienced the same impact. Some patients could still receive an alternative batch of the same drug before stocks were depleted. In such instances, the majority of patients were required to switch to a different brand or drug within the same or another drug class, depending on the nature of the recall. Last, for four combined patient populations, variations in the expected implications existed among the involved MAHs. We determined the impact that applied to the majority of patients for each combined drug recall. Although this approach may have resulted in an overestimation of certain impacts and an underestimation of others, we posit that these estimates bear limited relevance given their inherent variability. Despite these limitations, our study is the first to assess and quantify the impact of drug recalls on patients.

Our study contained several strengths. Specifically, we merged and validated the recall registration of three different organizations that resulted in a representative overview of drug recalls affecting patients in the Netherlands. Nevertheless, while the present retrospective analysis provided a reasonably comprehensive overview of drug recalls, we advocate for relevant (national) authorities to develop an easily accessible overview of drug recalls to effectively monitor the impact of drug recalls on patients. Moreover, we used

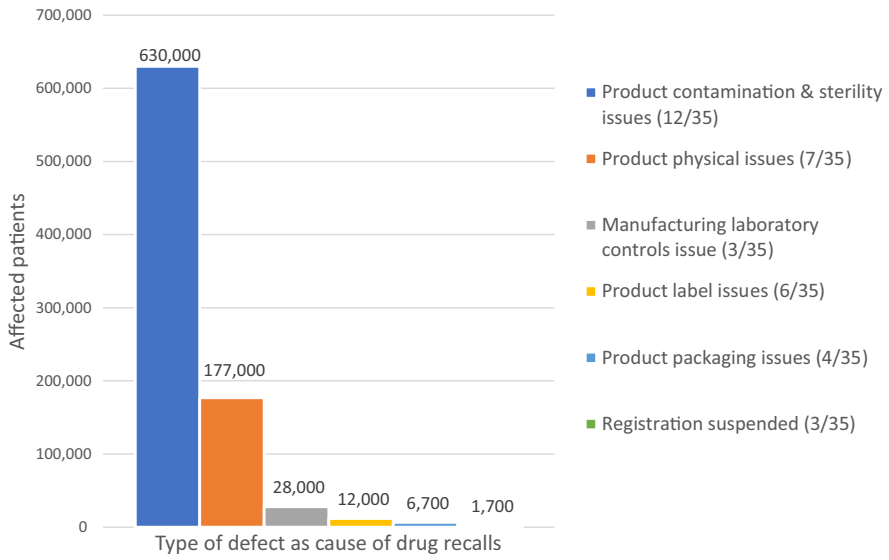

Figure 4 Defect description of drug recalls affecting patient populations.

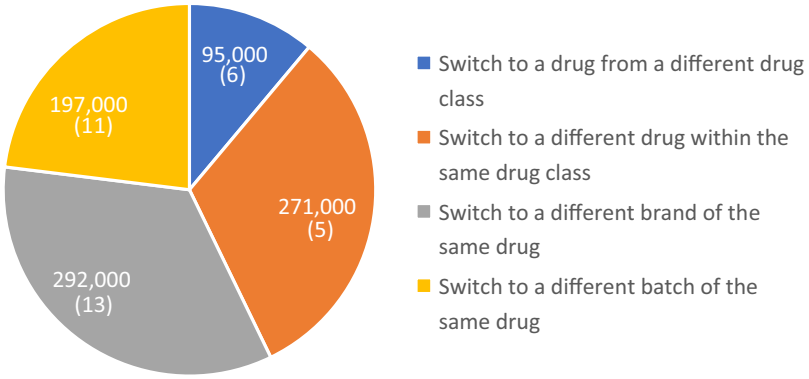

Figure 5 Patients affected by changes in medication as a result of drug recalls are divided into four categories. For each of the four categories, it is stated how many patients had to adjust their medication as a result of drug recalls as well as the number of patient populations (in brackets).

real-world drug dispensing data from SFK in combination with our compiled overview of drug recalls to assess the number of patients that were forced to actively switch their drugs.

Although our study has revealed a substantial number of affected patients, the potential implications of the existing recall handling and execution procedures on patient safety, trust in medication, and consequent medication adherence remain unknown since these research objectives were not part of this analysis. Furthermore, implementation of drug recalls also demands a considerable amount of effort and commitment from various stakeholders, including healthcare professionals, regulatory agencies, and MAHs. Pharmacy staff is tasked with the identification, notification, and counseling of patients affected by a drug recall. Similarly, physicians and other prescribers are required to invest their time and expertise in informing and advising patients as well as prescribing suitable alternative drugs if necessary. Future research should focus on elucidating the experiences of not only patients but also physicians, pharmacists, and other stakeholders with drug recalls as well as ascertaining patient and healthcare provider preferences concerning drug recalls.

In conclusion, this study showed that, spanning a 5-year period, 48 drug recalls necessitated patients to switch their drugs 855,000 times. Predominant factors leading to such drug recalls were product contamination and sterility issues. In the majority of cases, affected patients had to switch to an alternative brand of the same drug.

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CONFLICT OF INTEREST

M.L.B. is a member of the Dutch Medicines Evaluation Board (MEB). R.J.v.M. was a member of the Dutch MEB until September 1, 2023. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

P.A.A., H.J.D., M.L.B., and R.J.v.M. wrote the manuscript, designed the research, performed the research, and analyzed the data.

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