Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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RESEARCH NOTES

Drug and medical device product failures and the stability of the pharmaceutical supply chain

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ABSTRACT

Objective: Our objective was to review recent drug and medical device recalls, categorize recall types based on the free text descriptions posted within the recall announcements, and conduct exploratory analyses for researchers interested in pharmaceutical supply chain challenges.

Methods: A cross-sectional study of all current recalls, market withdrawals, and safety alerts published by the United States Food and Drug Administration pertaining to drugs was conducted. A manual review of all the recalls was also conducted to extract additional information including company details, recall type (labeling or quality), and location of failure in the pharmaceutical supply chain (manufacturing or distribution). Descriptive statistics and exploratory bivariate analyses were conducted to test any potential differences between drug and device recalls.

Results: Most recalls issued between January 2017 and September 2019 were pharmaceutical drug recalls (85.2%), while 34 (14.8%) medical device recalls were issued for the same period. For drug recalls, 85.1% (166/195) were because of quality, while 14.9% (29/195) were because of labeling issues. Of the quality issues for drug recalls, lack of sterility was the most frequent issue (139/166, 83.7%). There was no difference between drug or device recalls based on recall type ($P = 0.16$), top 20 pharmaceutical company ($P = 0.62$), or location of the supply chain failure ($P = 0.20$).

Conclusions: This study provides a process to categorize and evaluate drug and device recalls by recall type and location of the supply chain. By categorizing the free text provided in public recall data it would be easier to monitor trends over time.

In the United States, over 45% of Ame1ricans take at least 1 prescription medication.[1] To ensure product safety, the U.S. Food and Drug Administration (FDA) requires manufacturers to use Current Good Manufacturing Practices for the production of both drugs and medical devices.[2] However, even with this regulation in place there were over 70 recalls issued per year between 2017 and 2019.[3] Without proper identification of supply chain shortcomings, appropriate recalls may be delayed, jeopardizing the health of many Americans. The supply chain process varies largely between product types (drug and device) and even within a product group.[4]

Today, foreign outsourcing of a company's manufacturing process is more popular than ever, but this effort to cut costs comes at a price.[5] As the complexity of the supply chain increases, proper regulation and maintenance of high quality becomes more challenging. The nuances of globalization of the pharmaceutical supply chain have become more important with the spread of coronavirus disease.[6] With a large proportion of medications produced outside of the United States, manufacturing and shipping disruptions could create additional shortages. Recently, the American Pharmacists Association House of Delegates passed a policy supporting the protection of pharmaceuticals as a strategic asset, including the development of redundancies in the manufacturing processes to ensure reliable availability of high quality products, greater transparency, and timely information regarding shortages or product quality issues, and advocating for

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regulator and market incentives that bolster availability, quality, and safety of pharmaceuticals and other medical products (Figure 1).[7]

FDA currently communicates recall information, but how that information is categorized and evaluated is less understood. Our objective was to review recent drug and medical device recalls, categorize recall types based on the free text descriptions posted with the recall announcement, and conduct exploratory analyses for researchers interested in pharmaceutical supply chain challenges.

Methods

Using the publicly available recall information published by FDA, we reviewed drug and medical device recalls in the United States from January 2017 to September 2019. FDA further classifies drugs into several categories: animal, biologic, dietary supplement, generic, herbal, nutritional supplement, over-the-counter (OTC), physical medicine, or prescription, but for our analysis we grouped them all as drug recalls.[3] For each medical device and drug recall we extracted the company name, product description, product type, and recall reason description from FDA's Recall List.[3] We gathered additional background information on each company listed from their publicly available website. A company was considered as a consensus top 20 pharmaceutical company if it had a market capitalization and revenue (2018 fiscal year) that was within the top 20 among all the pharmaceutical companies. Subsidiaries of the consensus top 20 pharmaceutical companies were also considered to be a part of the list. We obtained the market capitalization and revenue data from each respective company's website and through the use of Bloomberg's company quote search feature.[8]

For each recall, we further categorized the recall type based on the description provided. On the basis of recall descriptions for all drugs and devices, we first created a dichotomous recall type variable reflecting "Labeling Error" and "Product Quality Issue" to differentiate between recalls where the product was manufactured properly but mislabeled and recalls where the product was adulterated or packaged incorrectly. Given the differences in product quality descriptors between drugs and devices, we created different subcategories to further qualitatively describe the recall types. For drug recalls, subcategories for product quality included general quality issue, sterility, potency, unapproved substance, and packaging. A general quality issue was a unique recall that did not fall under any of the other product quality subcategories that are mentioned. For example, recall owing to the lack of quality assurance for Synergy Rx Pharmacy's product paliperidone and lack of adequate controls for multiple homeopathic products from MBI Distributing Inc were both classified as general quality recalls. In contrast, the other product quality subcategories described specific recall circumstances. We defined a recall within the sterility subcategory if there was a lack of sterility assurance for the product or if an undeclared substance was present. In contrast, a recall was defined within the potency subcategory if there was either subpotency or superpotency of the drug, while the drug recall fell under the unapproved substance subcategory if a substance banned by FDA was present in the product. Finally, a recall was listed under the packaging subcategory if the product sequence was incorrect or there were missing tablets or capsules. Unlike the drug recalls, medical device recalls only described a general product quality issue or a labeling error. Categorization was conducted by one reviewer (ANL) and then was reviewed by a second reviewer (TJM) for general agreement. Any disagreements were discussed until consensus was reached. In addition, we determined where in the supply chain (manufacturing-level or distribution-level) the drug or device recall occurred by analyzing data available on FDA's website.

Protecting Pharmaceuticals as a Strategic Asset

1. APhA asserts that the quality and safety of pharmaceutical and other medical products and the global pharmaceutical and medical product supply chain are essential to the United States national security and public health.
2. APhA advocates for pharmacist engagement in the development and implementation of national and global strategies to ensure the availability, quality, and safety of pharmaceutical and other medical products.
3. APhA calls for the development, implementation, and oversight of enhanced and transparent processes, standards, and information that ensure quality and safety of all pharmaceutical ingredients and manufacturing processes.
4. APhA calls on the federal government to penalize entities who create barriers that threaten the availability, quality, and safety of United States pharmaceutical and other medical product supplies.
5. APhA calls for the development of redundancy and risk mitigation strategies in the manufacturing process to ensure reliable and consistent availability of safe and high-quality pharmaceutical and other medical products.
6. APhA advocates for regulatory and market incentives that bolster the availability, quality, and safety of pharmaceutical and other medical products.
7. APhA calls for greater transparency, accuracy, and timeliness of information and notification to health care professionals regarding drug shortages, product quality and manufacturing issues, supply disruption, and recalls.
8. APhA encourages pharmacy providers, health systems, and payers to develop coordinated response plans, including the use of therapeutic alternatives, to mitigate the impact of drug shortages and supply disruptions.
9. APhA supports federal legislation that engages pharmacists, other health professionals, and manufacturers in developing a United States-specific essential medicines list and provides funding mechanisms to ensure consistent availability of these products.
10. APhA recommends the use of pharmacists in the delivery of public messages, through media and other communication channels, regarding pharmaceutical supply and quality issues.

Figure 1. American Pharmacists Association policy statements issued in 2020, related to protecting pharmaceuticals as a strategic asset.[7] Abbreviation used: APhA, American pharmacists association.

Table 1
Comparison of drug and device recalls reported from 2017 to 2019

Total FDA recalls (n = 229)	Drug recalls N = 195 (%)	Device recalls N = 34 (%)	*P* value
Consensus top 20 company	—	—	—
Yes	28 (14.4)	6 (17.6)	—
No	167 (85.6)	28 (82.4)	—
	—	—	0.619
Recall type	—	—	—
Quality	166 (85.1)	32 (94.1)	—
Labeling	29 (14.9)	2 (5.9)	—
	—	—	0.157
Location of failure in the supply chain	—	—	—
Manufacturing	186 (95.4)	34 (100.0)	—
Distribution	9 (4.6)	0 (0.0)	—
	—	—	0.201

Abbreviation used: FDA, Food and Drug Administration.

Descriptive statistics for all variables were conducted and exploratory chi-square was performed to compare drug and device recalls.

Results

There were 195 (85.2%) drugs and 34 (14.8%) medical devices recalled by FDA in the United States from January 2017 to September 2019. These recalls mostly occurred within smaller companies, but 28 (12.2%) drug recalls were issued against a consensus top 20 pharmaceutical company.

Of the 195 drug recalls, 166 (85.1) were categorized as a quality issue whereas all but 2 (32 [94.1%]) of the medical device recalls fell under this category (Table 1). This meant that most of the recalls for both drugs and devices were because of product quality issues. Whereas we were only able to describe device recalls as a general quality issue or a labeling issue, drug recalls included enough information to generate subcategories (e.g., general quality, sterility, potency, unapproved substance, packaging). Most drug recalls defined as a quality issue (139/166, 83.7%) were further categorized in the lack of sterility subcategory. The percentage of medical device recalls that were issued toward a consensus top 20 pharmaceutical company was slightly higher (6 [17.6%]) than those issued for drug recalls (28 [14.3%]).

Between drugs and devices, there was no statistical significance ($P = 0.618$) in the number of consensus top 20 companies that were issued recalls. There was also no statistical significance ($P = 0.157$) between the number of quality and labeling recalls issued for drugs and devices. There was also no statistical significance ($P = 0.201$) regarding the location of the supply chain failure (Table 1).

Discussion

In this pilot study, we reviewed and categorized FDA drug and device recalls using free text publicly available within each specific recall (1) to determine whether this type of categorization was feasible, and (2) to assess our initial hypotheses that recall types would vary between drugs and devices. In this sample we found that quality issues were the most frequent type of recall for both the groups, and we were unable to determine any significant differences between drugs and devices with other select variables (e.g., top 20 company and location of the failure in the supply chain). We did feel that this pilot demonstrated that the free text fields within FDA recall announcements provide valuable information that could be further categorized using qualitative analysis and that natural language processing (NLP) methods may be warranted for more efficient categorization.

Medical device recalls were only a small proportion of the recalls found in our analysis, but further examination in device manufacturing may be warranted. The 510(k) provision allows for Class I or II medical devices to be approved without clinical trials or manufacturing inspections of safety and efficacy.[4] Premarket approval costs for Class I and II medical devices are significantly cheaper ($18,200 vs $870,000) than the premarket approval process used for Class III medical devices.[4] In addition, medical device recalls are often very costly and deadly for the consumer because they are largely used *in vivo*. When a quality recall is issued for an in vivo medical device a separate operation to fix the device has to occur putting unnecessary risk and financial burden on the consumer. For researchers interested in applying NLP methods to recalls, device, recalls may be more difficult to apply NLP algorithms due to the fewer number of recalls available to assess.

This pilot study had several limitations as our focus on categorizing all types of drugs into different categories may have oversimplified the information available in each recall. We did not report discordant pairs to represent the disagreement frequency in our categorization which may limit the validity in our categorization process. However, we justified this approach with a small sample because we were able to discuss all of the recalls to reach full consensus. In addition, our initial analysis only focused on the recall data and did not consider searching for adverse events reported in the news or through the FDA Adverse Event Reporting System. In addition to adverse events, which have a direct effect on clinical outcomes, supply chain disruptions (shortages) may provide another area for potential research as these events might have direct and indirect effects on patient outcome. In either case, future research focusing on actual clinical harm or poor outcomes, experienced by patients, associated with drug and device recalls may be more useful to guide policy or regulatory action. Finally, FDA further classifies "drugs" into more specific subgroups, but given the small sample of all drug recalls in this period we chose not to use the smaller groupings (e.g., animal, biologic, dietary supplement, generic, herbal, nutritional supplement, OTC, physical

medicine, or prescription). A more in-depth analysis of these individual categories may be necessary for future work.

Conclusion

Most recalls for both pharmaceutical drugs and medical devices from 2017 to 2019 were issued owing to quality issues, specifically sterility issues during the drug supply chain. Given the availability of free text data within FDA recalls posted for the public, the development of predictive analytics using key word phrases or NLP may improve the efficiency for reviewing unstructured data to provide in-depth information about what actually happened. By determining product failures in the supply chain, FDA can focus resources on specific areas which will save both time and costs.

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