MEDICINE RECALL SYSTEMS IN THE USA AND EU: A REGULATORY COMPARISON

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Abstract

Medicine recall was an essential regulatory mechanism designed to protect patients from medicines that were unsafe, ineffective, or of poor quality. It involved the removal of specific batches or lots of medicinal products due to issues such as manufacturing defects, contamination, or labeling errors, whereas withdrawals referred to the permanent removal of an entire drug product from the market. The reasons for medicine recalls varied and, depending on the level of risk to patients, recalls were carried out at different levels of the supply chain, ranging from distributors and pharmacies to patients themselves. The aim of this study was to analyze and compare how this system was organized in the United States and the European Union. The methodology was based on the analysis of scientific literature and statistical data obtained from official reports of the U.S. Food and Drug Administration and the European Medicines Agency. The findings indicated that, despite differences in structural organization, implementation, and levels of transparency, both regulatory systems aimed to protect patients and ensure the quality and safety of medicines. The study highlighted that effective recall procedures and regulatory coordination played a crucial role in minimizing risks associated with defective medicinal products. Overall, continuous improvement in recall mechanisms, strengthened regulatory cooperation, and compliance with relevant standards and regulations by pharmaceutical companies were essential for enhancing pharmaceutical safety at both national and international levels.

Keywords: medicine recalls, quality , safety, FDA, EMA,

Introduction

The quality and safety of medicines are one of the main pillars of the health system that have a direct impact on the health of the population (Rasheed *et al*.,2023). Therefore, every medicine to be introduced into the market must have marketing authorization, after its quality, safety and efficacy have been assessed, and after the benefit-risk balance is considered positive (Aronson *et al*, 2017). Usually, marketing authorization is granted for a certain period with the possibility of renewal (EMA, 2026). But even during this period, medicines are usually monitored by the competent regulatory authorities to ensure whether they meet the requirements in terms of quality, efficacy and safety. Even in cases where a medicinal product has been authorized for many years, new information may eventually emerge requiring its recall or withdrawal from the market, because it no longer meets quality requirements, for example due to the unexpected identification of impurities, other quality defects, or adverse effects.

Therefore, medicine recalls are a necessary mechanism to protect patients from medicines that may be unsafe, ineffective, or poor quality. Drug recalls are a regulatory mechanism used to remove specific batches or lots of medication due to manufacturing defects, contamination, or labeling errors, while withdrawals involve the permanent removal of entire drug products from the market (Patel *et al*,2023)

The reasons for recalls of medicine can be numerous, such as the presence of impurities, deviations in content, physical defects of the product, irregularities, suspicions related to

packaging and labeling, as well as the occurrence of unexpected side effects. Depending on the level of risk of the pharmaceutical product irregularities, recalls can be carried out at different levels of the supply chain, ranging from distributors and pharmacies to patients. Therefore, competent pharmaceutical regulatory authorities have organized the medicine recall system at local, regional, and global levels. The absence of such a system would create the possibility for defective medicines to circulate and be used in the market, increasing the risk of serious side effects, treatment failure, and potential public health crises.

Recalls of medicine also have legal and economic implications for pharmaceutical companies, as well as affecting the trust of patients and healthcare professionals in medical products (Trevir & Nath., 2019). Besides their protective role, recalls also serve as an important tool for the continuous improvement of the pharmaceutical industry (Cheah *et al.,* 2007). They help in identifying deficiencies in manufacturing, storage, and distribution processes, encouraging the implementation of stricter quality control measures and higher safety standards Therefore, recalls are not only a response to existing problems but also a mechanism for preventing them in the future.

Evolution of medicine recalls

The development of mechanisms for medicine recalls is closely related to the evolution of pharmaceutical regulation and increasing awareness of patient safety. In the early years of the pharmaceutical industry, the lack of manufacturing standards and quality control often allowed unsafe products to enter the market (Schmidt, H., & Huber, F., 2021). As a result, interventions to remove suspicious and unsafe drugs from the market were rare, uncoordinated, and usually occurred only after adverse effects had become apparent.

Several landmark drug safety incidents played a crucial role in highlighting the need to strengthen pharmaceutical regulations worldwide to ensure greater safety in the use of medicines. One of the earliest and most significant cases is the Elixir Sulfanilamide incident in 1937 , where the use of a toxic solvent in the product's formulation resulted in the deaths of over 100 people, mainly children (*Sulfanilamide Disaster*., 2024) .This incident was the result of inadequate testing, insufficient quality control systems, and the absence of stricter drug regulations before being released to the market. Another significant event is the thalidomide tragedy in the late 1950s and early 1960s. (Yashiro *et al*., 2018). The drug, which was widely used by pregnant women to relieve nausea, led to the birth of thousands of babies with severe congenital malformations. This case highlighted the importance of carefully testing and monitoring side effects of medicines across different population groups and led to stronger requirements for clinical trials and post-marketing drug surveillance.

These cases demonstrate that medicines can be dangerous without proper testing, and that it is not sufficient for only the active substance to be effective, as all other ingredients must also be proven safe .They also highlighted the need for a system that allows the rapid recall of suspicious and dangerous products. Following these events, the roles of regulatory authorities such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) were strengthened, leading to the development of more structured systems for continuous drug monitoring through recalls. These systems include classification of recalls based on risk level, clear communication procedures, and coordination between manufacturers, distributors and healthcare professionals.

In recent decades, the globalization of the pharmaceutical market and the increasing complexity of the supply chain have created new challenges in the management of drug recalls. However, advances in technology, the development of pharmacovigilance systems and greater institutional transparency have significantly improved the ability to detect problems and intervene in a timely manner (Fadare, J. O., *et al.* ,2023). As a result, drug recalls have evolved from reactive measure into a key component of a proactive system for ensuring the safety and quality of medicinal products.

Classification of recalls

There are two types of recalls depending on the source of initiation, namely who initiates the process and the extent of state authority involved (Shevale *et al,* 2014; Meghan Lehmann *et al., 2010;* Guidelines on Recall and Rapid Alert System for Drugs, CDSCO ,2012):
Voluntary recall – initiated by the pharmaceutical company itself (manufacturer or distributor) when a problem or irregularity is identified in certain batches of a pharmaceutical product, such as quality defects, incorrect labeling, or other issues that may pose a risk to patients' health. In such cases, the regulatory authority (FDA, EMA or national Agency of Medicine) may request or recommend the recall of a product. This represents one of the most common forms of recall.
Mandatory recall – is less common and occurs only in serious cases when a product poses a risk to health and may cause serious injury or death. This typically happens when a product or batch does not meet required quality standards, when medicines are prohibited for use, or when labeling and promotional materials violate applicable laws and regulations. In these cases, the competent regulatory authority orders the product to be recalled from the market, either at the central or local level.
The categorization of recalls into "voluntary" and "mandatory" is formally applied in the United States by the FDA, where these terms are defined within a legal framework. In the European Union, although recalls in practice may be initiated by companies or requested by regulatory authorities, there is no formal legal classification of recalls in EU legislation. Instead, the EMA and the national authorities of each Member State focus on legal obligations, risk assessment, and risk management rather than on the "voluntary" or "mandatory" classification of recalls.

[1] Recalls are classified into three categories based on the level of health risk (FDA,2026):
Class I (major): These are the most serious recalls, where there is a reasonable probability that the use of, or exposure to, the recalled drug will cause serious adverse health consequences or death. In such cases, the effects may be immediate and life-threatening. Class I recall is urgent and typically involves removing the product from the market, often extending to the consumer level.
Class II (moderate): The use of the drug may cause temporary or medically reversible adverse health consequences, while the probability of serious harm is low. These recalls are usually carried out at the retail level, and patients may continue using the medicine unless otherwise advised by the company or the competent regulatory authority.
Class III (minor): The use of the drug is unlikely to cause adverse health consequences. These recalls typically involve issues such as minor labeling errors, packaging defects, or incorrect expiration dates. They are usually carried out at the distribution (wholesale) level, and patients

may continue using the product unless otherwise instructed by the manufacturer or the relevant authority

The classification of recalls into Class I, II, and III is used in United States (FDA,2026), whereas in the European Union recalls are managed through a risk-based approach assessed on a case-by-case basis, without a standardized classification system. In the EU (EMA), there is no formal legal classification of recalls; instead, each case is evaluated individually based on the severity of the risk, the likelihood of harm, and the urgency of action.

However, EMA statistical reports may still present data using Class I, II, and III categories for analytical purposes, mainly to facilitate comparison and statistical reporting. These classifications are therefore used only for data presentation and do not represent a formal regulatory system within the European Union, whereas in the United States, these classes form part of a formal regulatory framework used by the FDA to assess and communicate risk levels.

Comparison of the recall systems in the USA and the EU

The medicine recall systems in the United States and the European Union have been established to ensure patient safety by removing defective or potentially hazardous pharmaceutical products from the market. Although both systems share the same primary objective of protecting patients through the removal of unsafe medicines, they differ in terms of organizational structure, implementation, and levels of transparency (Bigoniya *et al*, 2018)

One of the main differences relates to the regulatory structure. In the United States, medicine recalls are centrally managed by the FDA, which provides a unified and standardized approach. In contrast, in the European Union, the system is more decentralized and involves the EMA as well as the national Medicines Regulatory Authorities (MRAs) of each Member State. This makes the European system more complex but also more flexible.

Regarding the initiation of recalls, in both systems they are often initiated voluntarily by pharmaceutical companies. However, in the United States, the FDA plays a more direct and visible role in oversight, whereas in the European Union, the process is often initially coordinated at the national level and then communicated among Member States, regardless of the recall class.

An important difference can also be observed in terms of transparency and access to data. In the United States, the FDA provides a centralized and publicly accessible system for recalls (e.g., the FDA Recall Database and Enforcement Reports), which enables detailed statistical analysis. In the European Union, however, there is no single centralized public database. Instead, information is typically provided through national authorities, making data collection more challenging. Recall data are not consolidated in a single source but are instead distributed across various platforms, such as inspection reports, pharmacovigilance systems, and rapid alert systems. As a result, statistical analysis is more complex compared to the U.S. system.

There are also differences in terms of coordination and response. The European Union uses the Rapid Alert System to ensure immediate communication among Member States, especially in high-risk cases (Class I). In the United States, communication is more centralized and direct due to the presence of a single authority, namely the FDA, which coordinates and manages the recall process at the national level. This centralization enables a faster and more unified response in managing high-risk cases.

Statistical data regarding recalls

Statistical data on drug recalls in the United States and the European Union were obtained from various regulatory and reporting sources. For the USA, data from the FDA Recall Database covering the period from 2012 to 2023 were used, along with information from annual reports and published studies. For the European Union, data were taken from the annual reports of the European Medicines Agency (EMA), focusing on quality defects and recalls for the period 2020–2024 (Ema, 2024)

Based on FDA Recall Database, as well as a study (Patel et al., 2024) covering the period 2012–2023, a total of 15710 drug recalls were recorded. Of these, 1524 were classified as Class I recalls, 12679 as Class II, and 1507 as Class III recalls, initiated by pharmaceutical companies (Figure 1).

The reasons for drug recalls were also analyzed, and five main categories were identified: production problems, sterility issues, out-of-specification (OOS) results, contamination, and labeling problems. It was observed that a total of 5766 recalls were due to lack of sterility assurance, while 3195 were related to non-compliance with current Good Manufacturing Practices (cGMP). A further 2117 recalls were associated with OOS results, 1712 with contamination (mainly microbiological), and 1274 with labeling errors, including incorrect or missing expiration dates and label mix-ups. In addition, 833 recalls were related to packaging and storage issues, 300 to adverse reactions, 276 to marketing without prior regulatory authorization, and another 276 to miscellaneous reasons, including non-compliance with United States Pharmacopeia specifications, product crystallization, inaccurate dosing systems due to calibration errors, and failures to meet pharmacopeial monograph requirements (Figure 2).

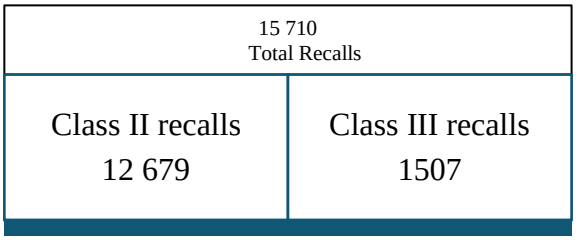

Figure 1. Categorization of all drug recalls issued by the FDA from June 2012 to August 2023

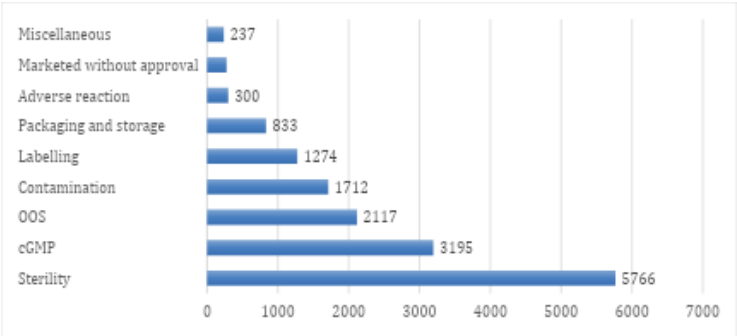

Figure 2. Categorization of drug recalls issued by the FDA from 2012 to 2023 according to their main reasons

The FDA issued many recall notifications to pharmaceutical manufacturers during the period from 2012 to 2023, mainly due to issues related to current Good Manufacturing Practices (cGMP) and sterility. Figure 3 presents the number of recalls per year over the 10-year period,

categorized according to several key causes, including sterility, out-of-specification (OOS) results, labeling issues, cGMP non-compliance, and contamination

The study shows that the main causes of drug recalls in the United States (2012–2023) are issues related to sterility and cGMP non-compliance, with lack of sterility assurance and non-sterility constituting most cases. Other causes include storage-related issues, manufacturing issues, and product impurities. Therefore, pharmaceutical companies should improve compliance with quality standards and implement effective quality management systems that oversee production processes, quality control, staff training, and documentation to prevent future drug recalls.

According to data from the European Medicines Agency (EMA, 2024), the number of notifications related to quality defects showed a continuous increase during the period 2020–2024, rising from 170 in 2020 to 395 in 2024 (Figure 4).

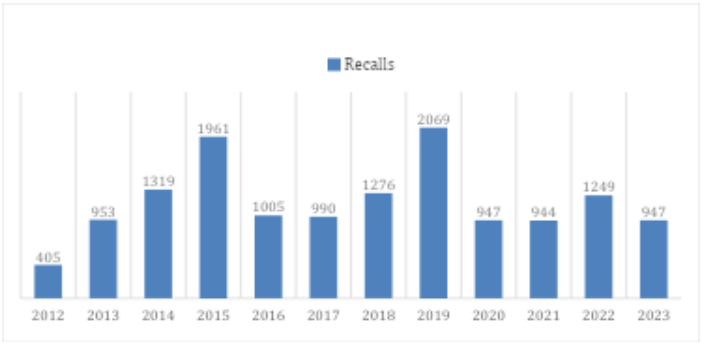

Figure 3.Number of recalls for each year in the period 2012 -2023

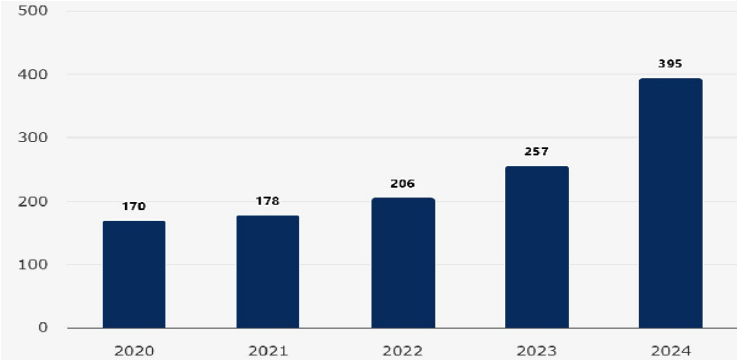

Figure 4.Number of quality defect notifications received (Source: EMA annual report 2024)

The number of confirmed quality defect cases is lower, reflecting the fact that not all suspected reports are confirmed as actual defects after investigation (Fig.5). In 2024, out of 395 notifications received, 221 cases were confirmed as actual quality defects. This discrepancy indicates that a considerable proportion of initial reports do not meet the criteria for classification as confirmed defects. However, the confirmed cases resulted in recalls of batches for nine centrally authorized products (CAPs), with no cases classified as Class I recalls, indicating that there was no immediate risk to life. In 2020, there were 15 recalls reported, of which 3 were Class I and 3 were Class II , while 9 recalls were Class III . In 2021, there were 164 confirmed cases of quality defects, of which 10 resulted in recalls, including 1 recall as a Class I , 7 recalls were Class II , and 2 recalls were Class III . During 2022, there were 185 confirmed cases of quality defects, of which 11 resulted in recalls, including 2 as Class I , 5 recalls as Class II , and 4 recalls as Class III . In 2023, there were a total of 188 confirmed

cases of quality defects, of which 9 resulted in recalls, including 6 recalls as Class II , 2 recalls as Class III , and 1 unclassified recall (Fig.5). This reporting demonstrated the importance of the verification process within the pharmacovigilance system, where only confirmed defects initiated regulatory actions such as medicine recalls.

In 2024, the main reasons for the recalls of centrally authorised products (CAPs) included several major categories of quality defects. Among them, issues related to laboratory and production control processes were among the most frequently reported, including results outside specified limits during quality control testing. Another important category was contamination and product sterility issues, including chemical, microbiological, or physical contamination of drugs. Labelling problems were also identified, such as missing or incorrect batch numbers. In addition, recalls were caused by packaging defects, including physical issues such as mixed packages or damaged containers. Finally, problems related to the physical properties of products were reported, such as tablet hardness, size, and shape.

In general, data from the EMA and FDA indicate an increase in reports of quality defects, but a low level of serious risk to patients. Most of the issues are technical in nature and are detected through control and monitoring systems, reflecting the effective functioning of regulatory mechanisms in ensuring the safety of medicines on the market.

	2020	2021	2022	2023	2024
Quality defects confirmed cases		164	185	188	221
Recalls	15	10	11	9*	9
Class 1	3	1	2	0	0
Class 2	3	7	5	6	5
Class 3	9	2	4	2	4

*1 recall not classified

Figure 5. Quality defects confirmed cases and categorization of recalls (source : EMA annual report 2024)

Minimizing drug recalls

Drug recalls can negatively impact the financial performance of pharmaceutical companies and reduce their reputation and patient trust. Pharmaceutical companies can minimize these recalls through several measures (Nagaich *et al.*, 2015):

1. Compliance with regulations and standards
2. Legal and brand protection through rapid response
3. Improvement of production process efficiency
4. Improved data management through closed-loop decision-making systems
5. Strengthening product quality control systems
6. Increasing operational transparency
7. Enhancing accountability through automated auditing

All these measures not only help to minimize recalls but also contribute to improving the quality and safety of medicinal products.

Conclusion

The recall of medicines is a key component of the pharmaceutical safety system, playing a dual role: the immediate protection of patients and the long-term improvement of medicinal

product quality. This study highlights the importance of medicine recall systems in both the United States and the European Union, with emphasis on their regulatory differences and operational approaches. Understanding this process and its impact is essential for the development of effective health policies and for enhancing patient safety. Overall, continuous improvement in recall mechanisms and regulatory cooperation is essential for strengthening pharmaceutical safety at both national and international levels

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