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REVIEWS

POST-MARKETING DRUG WITHDRAWALS: A REVIEW

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The emergence of new diseases demands high-speed drug development. Drug development is a long and tedious process. As research for medicine goes on several changes occur in the process of drug development. In order to promote safe and proper use of drugs with the fewest side effects, black box warnings are given to the drugs. Many times, these drugs must be removed at the final stage of marketing owing to the many adverse effects found during drug development. Hence, it is important for every newly developed drug to be safe for people and ideally to have no side effects. This review describes the black box warnings issued by the Food and Drug Administration (FDA) for certain drugs and the reasons for some of the post-marketing drug withdrawals. Most of the post-marketing drug withdrawals are a result of unanticipated or unprecedented adverse drug effects.

Keywords: drug development; adverse drug response; black box warning; post-marketing drug withdrawal; efficacy; drug labeling; food and drugs administration

INTRODUCTION

Efficacy and safety are critical aspects that influence the viability of the chemical entity as it progresses through the drug development process. However, after receiving regulatory approval, several new chemical entities (NCEs) have been withdrawn from the market. Inefficiency, severe side effects, and financial and regulatory issues are only a few of the reasons for these problems. Adverse drug responses (ADRs) are responsible for not just market withdrawals but also prescription drug labels being changed, and new black-box warnings being added [1].

Individual case reports or case series, observational studies, randomized comparisons, or systematic reviews can all lead to the post-marketing withdrawal of a pharmaceutical product owing to drug-related deaths. The withdrawal of products from the market because of deaths can be contentious, especially when there is no direct link between drug usage and death. Weak incentives can also result in significant financial losses for manufacturers [2].

Drug development

Drug development is the process that takes 12–15 years, many failures, and much uncertainty. It can cost more than $1 billion from the initial concept to the release of a finished product [3].

The stages of drug discovery, design, and development are shown in Figure 1 and listed below.

1. Discovery and development
2. Preclinical research
3. Clinical development
4. FDA review
5. Post-marketing monitoring

1. Discovery and development

It includes target identification and validation as the first step. As a target, a gene or protein (therapeutic agent) that plays a significant role in disease is selected. Scientists and researchers then record the therapeutic characteristics of the target. Targets for drugs must be effective, safe, and useful, as well as meet clinical and commercial requirements. To validate targets, researchers use modern tools and techniques such as disease association, bioactive substances, cell-based models, protein interactions, signaling pathways analysis, gene functional analysis, in vitro genetic manipulation, antibodies, and chemical genomics.

2. Preclinical research

Preclinical research involves the testing of new drugs in terms of efficacy, toxicity, and pharmacokinetics on nonhuman subjects. Scientists conduct these investigations *in vitro*

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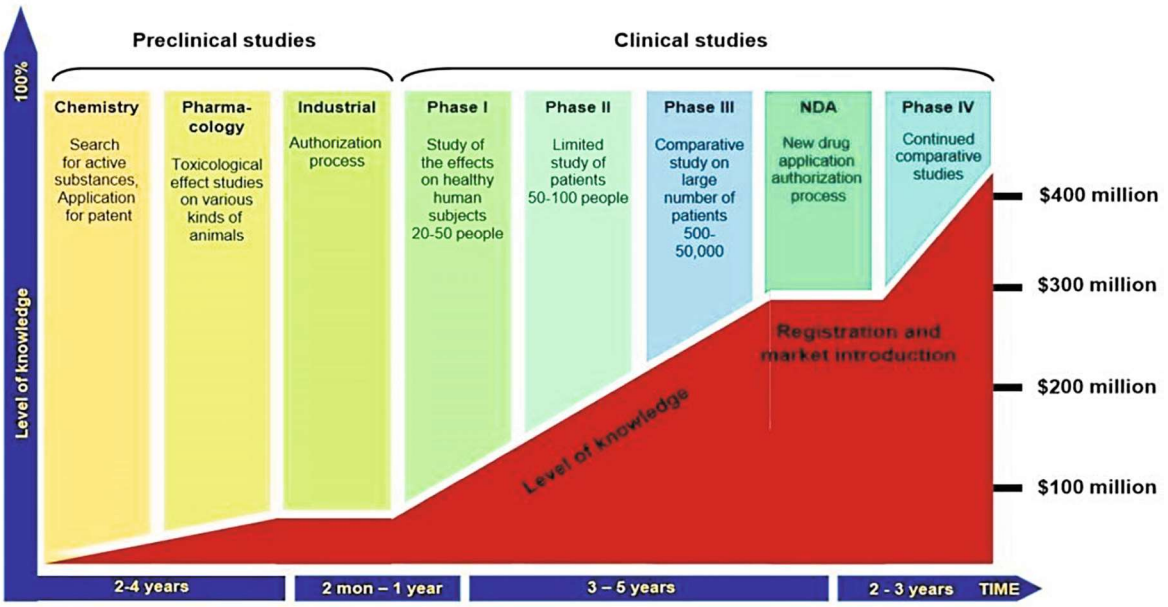

Fig. 1. Stages of Drug Development [4].

and *in vivo* with unrestricted dosages. The pharmacokinetics processes of measuring how a new drug affects the body are absorption, distribution, disposition, metabolism, and excretion. Each effect is mathematically described in this process.

3. Clinical development

Scientists move on to clinical drug development after finishing preclinical research, which involves clinical trials and volunteer studies to fine-tune the medicine for human usage. In clinical trials, dose progression, single ascending and multiple dosing investigations are performed to determine the correct patient dosage. The clinical drug development process includes four phases, as shown in Figure 2.

4. FDA review

The new drug is sent to the FDA for a thorough review once clinical trials are completed and the drug shows optimal efficacy and safety. The FDA evaluates the pharmaceutical application received from the drug development company and either approves or rejects it [3, 6].

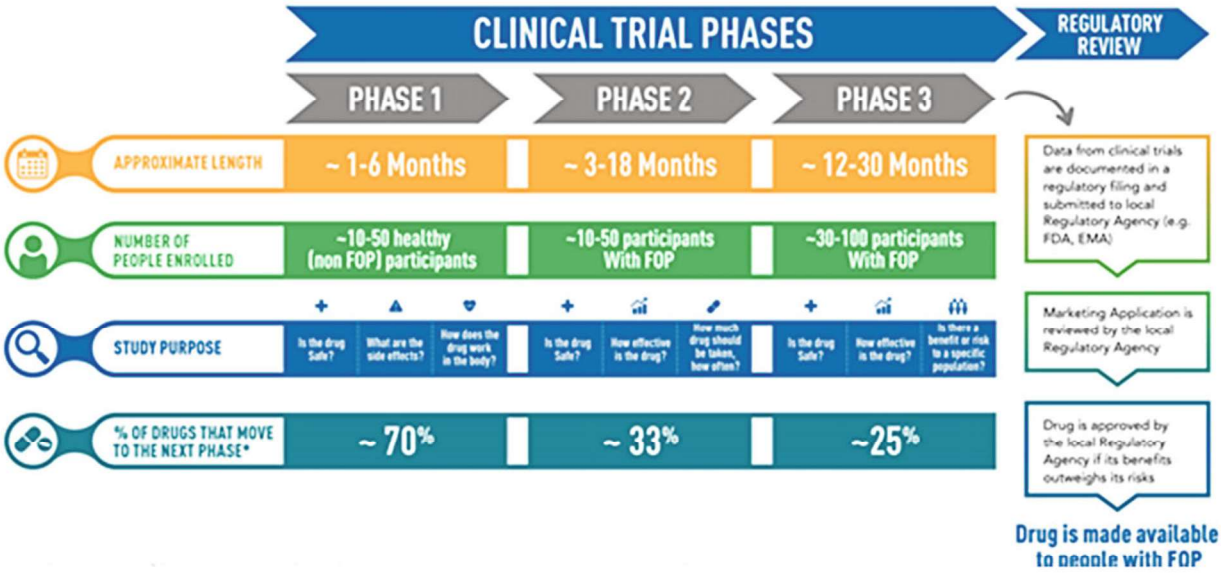

Fig. 2. Phases of a Clinical Trial [5].

Reason for drug failure

Toxicity, pH characteristics, poor drug performance, effectiveness, and bioavailability are the reasons for the failure of new drug applications.

Toxicity: If the toxicity of a novel medicine in human or animal patients is too high, it may be rejected owing to safety concerns with regard to its use after manufacture.

Pharmacokinetic characteristics or poor bioavailability: A failed FDA review can also be caused by low water solubility or rapid first-pass metabolism of the medication. Two pharmacokinetic causes of pharmacological failure are inadequate duration of action and unexpected human drug interactions.

Efficacy: The FDA may reject a novel medicine if its efficacy is insufficient, or the data are inconclusive.

Inadequate drug performance: The FDA may reject the application in favor of a better-performing formulation if the new medicine only partially satisfies the desired purpose [1].

(a) Adverse drug reaction

Any unfavorable impact of a medicine that occurs during clinical usage in addition to its expected therapeutic effects is referred to as an ADR. An adverse drug event is an undesirable occurrence that occurs after exposure to a drug but is not necessarily caused by the drug.

Because only about 1500 people are exposed to a pharmaceutical before it is marketed, nothing is known about its safety in clinical use. As clinical judgment is sometimes required for detection and diagnosis, a medication safety assessment should be considered an integral part of daily clinical practice [13].

Results of adverse drug reactions [7]

1. Accidental, harmful results linked to the use of drugs are the cause of and occur during a significant proportion of unexpected hospital admissions.
2. About 10–20% of hospital inpatients are affected.
3. Medical inpatients account for 0.1%, whereas surgical inpatients account for 0.01% of deaths.
4. Patient's quality of life is adversely affected.
5. Costs of patient care will increase.
6. It is possible that it will appear to be a disease, causing unnecessary investigations and treatment delays.

Why does ADR occur?

Most ADRs are caused by the desired pharmacological effects being prolonged, which is frequently due to high variability of pharmacokinetics and pharmacodynamics reported among patients. The pathogenesis of ADRs is affected by pharmacological, immunological, and genetic variables.

While taking high-risk agents, patient characteristics (gender, age, weight, creatinine clearance, and the number of diseases) as well as drug administration (dosage, administration route, and the number of concurrent drugs) should all be carefully monitored. Age, gender, multiple medications, disease status, a history of ADRs or allergy, hereditary factors, high doses, and a range of other factors can all increase the risk of ADRs. Drug discontinuance or dose modifications may influence the development of ADRs to some drugs in specific demographics, particularly the elderly [8].

Some ADRs can result from errors in the manufacture, supply, prescription, administration, or consumption of medications. In Harvard medical practice research, 18% of medicines were linked to carelessness, defined as failure to fulfil

TABLE 1. Application of pharmacogenomics in drug development stages [10]

Stage	*Application of pharmacogenetics/pharmacogenomics*
Drug target Identification	Identification and characterisation of the gene coding for the drug target and to assess the variability
Phase I clinical trial	Patient selection – Inclusion/Exclusion criteria
	Dose range selection
Phase II clinical trial	Dose modification
Phase III clinical trial	Interpretation of trial results based on pharmacogenetic test results
Phase IV clinical trial	Analysis of reported adverse events with pharmacogenetic tests
Regulatory issues	Requirements for submission of pharmacogenetic data during development by FDA
Patient therapeutics	Personalization of drug therapy
	Pharmacogenetic data in drug labelling
	Identification of responders and non responders
	Identification of high risk groups of adverse events

the level of care reasonably expected of a physician qualified to care for the patient, which was found to be the cause of ADRs. The five types of factors that influence the formation of ADRs are patient-related factors, social factors, drug-related factors, disease-related factors, and ADR-related factors [6].

Pharmacogenomics in Adverse Drug Reactions

Pharmacogenomics is a branch of science that studies how a person's genes impact how they respond to drugs. Studies on pharmacogenomics can be used at different stages of the drug development process. One can estimate and determine how drug target polymorphisms affect drug response. Pharmacogenetic testing can be used in clinical studies to categorize individuals according to their genotype, which reveals their ability to metabolize drugs. As a result, clinical trials turn out better and important adverse drug reactions are avoided [9]. Table 1 depicts the several applications of pharmacogenomics in drug development stages.

The primary purpose of genetic testing is to increase a person's drug response while simultaneously reducing the possibility that they will develop an ADR. A laboratory test must offer data that are relevant to the therapeutic choice to be clinically useful. The dosage of a particular medication, as well as a possible substitute, are relevant details because there may be contraindications or a poor response because of a specific genetic variation. Pharmacogenetic laboratory data help to classify individuals into several groups, including ultra-rapid metabolizers, normal metabolizers, and also poor metabolizers [11].

Pharmacogenomics can be useful in identifying drug responders and nonresponders, avoiding adverse drug reactions, and optimizing drug dosage, enabling personalized therapy. Pharmacogenomics can also aid in identifying the disease's pathogenic pathways. The currently available clinically relevant pharmacogenomic tests focus primarily on predicting medication toxicity and dose modification. More study will be required to determine the genetic factors that determine responders and nonresponders, particularly for medications used to treat prevalent complicated disorders [12].

Pharmacogenomic approaches can provide a more accurate prediction for individual drug response, which in turn can guide drug selection and dosage to achieve individualized drug therapy and avoid ADRs. The first genotype test approved by the FDA was the AmpliChip CYP450 test to determine the appropriate drugs and doses to prescribe by using a patient's genetic information. It can identify several polymorphisms, such as 36 polymorphisms of CYP2D6 (*1, *10A, *10B, *11, *15, *17, *19, *20, *29, *2A, *2B, *2D, *3, *40, *41, *4A, *4B, *4D, *4J, *4K, *5, *6A, *6B, *6C, *7, *8, *9, *1XN, *2XN, *4XN, *10XN, *17XN, *35XN, *41XN, *35, and *36) and two polymorphisms of CYP2C19 (*2 and *3) with regard to their role in the metabolism of amitriptyline, clomipramine, clopidogrel, codeine, desipramine, doxepin, esomeprazole, fluoxetine, imipramine, metoprolol, nortriptyline, omeprazole, paroxetine, phenytoin, risperidone, tamoxifen, and trimipramine. Recently, more pharmacogenomic tests have been approved, including CYP2C9, VKORC1, and SLCO1B1 genotyping for warfarin, amitriptyline, azathioprine, clomipramine, clopidogrel, codeine, desipramine, doxepin, fluoxetine, imipramine, mercaptopurine, nortriptyline, paroxetine, simvastatin, thioguanine, and trimipramine; DPYD, MTHFR (rs1801131 and rs1801133), and TYMS genotyping for capecitabine and fluorouracil; G6PD genotyping for dapsone, doxorubicin, flutamide, methylene blue, nalidixic acid, phenazopyridine, primaquine, rasburicase, sulfacetamide, sulfamethoxazole, and sulfanilamide; UGT1A1*28 genotyping for irinotecan; CFTR genotyping for ivacaftor; EGFR genotyping for erlotinib and gefitinib; KRAS mutations for cetuximab and panitumumab; ERBB2/HER-2 genotyping for trastuzumab (Herceptin); TPMT genotyping for azathioprine, mercaptopurine, and thioguanine; HLA-B*57:01, *58:01, and *15:02 genotyping for abacavir, allopurinol, carbamazepine, and phenytoin; IFNL3 (rs12979860 and rs8099917) genotyping for peginterferon a-2a, peginterferon a-2b, and ribavirin; FCGR3A (rs396991) genotyping for rituximab; and ABL1 genotyping for dasatinib, imatinib, and nilotinib. These tests will help to minimize human genetic variation-induced ADRs and prevent patients from being improperly treated with suboptimal doses. Although the association between genetic variations and the risk of ADRs has been observed, it still requires more clinical trials to validate such genetic variation–ADR association and determine whether pharmacogenomics is cost effective and benefits clinical therapy [13].

(b) Black-box warning

A black-box warning is the most serious warning issued by the FDA for drugs and medical devices on the market. Black-box warnings, often known as boxed warnings, notify the public and health care professionals about serious adverse effects, including injury or death. According to the FDA, drug companies must include a warning label on prescriptions that have a black-box warning.

When extreme adverse reactions or specific difficulties develop, such as those that may result in death or serious harm, the FDA adds a "black box" to the labeling of drugs or drug products. Black-box warnings are described under "Warnings (21CFR 201.57 (e))" in the Code of Federal Regulations (CFR). This part of the CFR states: "Labelling must indicate major adverse reactions and potential safety dangers, as well as the limitations in use that they impose and the actions that should be taken if they occur. When there is reasonable evidence that a drug is linked to a major hazard, the labelling must be updated to add a warning; a causal relationship does not need to be proven… *Special problems, particularly those that may lead to death or serious injury, may be required by the Food and Drug Administration to be placed*

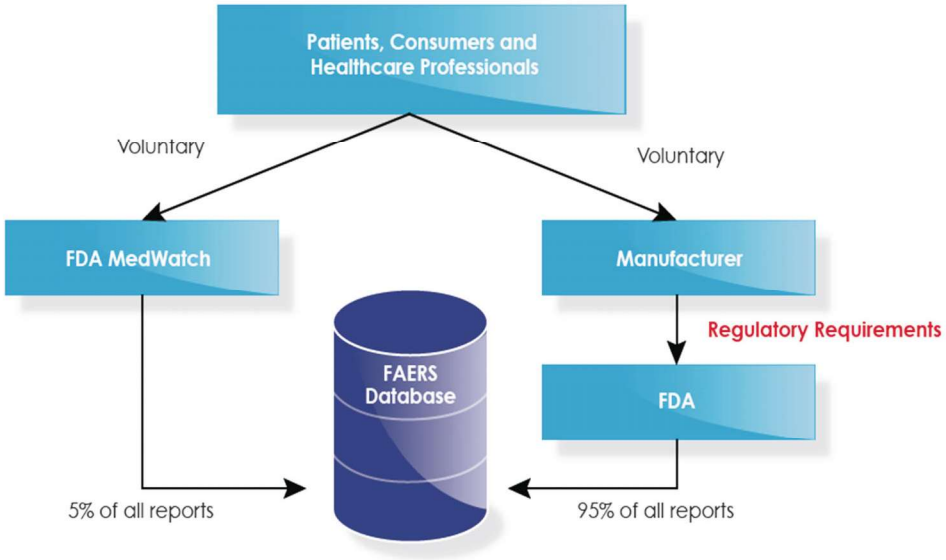

Fig. 3. Collection of a drug's post-marketing reports [16].

in a prominently displayed box. The boxed warning ordinarily shall be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data [emphasis added]. If a boxed warning is required, its location will be specified by the Food and Drug Administration" [14].

This is a major post-marketing safety action if these pharmaceuticals have ever received a post-marketing boxed warning or a withdrawal from the market owing to safety concerns. Other easily measurable data submitted to the FDA during the pharmaceutical review are rarely connected to post-marketing safety events [15].

The FDA's Black-Box Warning Process

The FDA requires evidence for a serious risk before adding a boxed warning to a pharmaceutical or medical device. Observations and research undertaken after a medicine has been on the market provide this evidence.

This implies that new pharmaceuticals that have recently hit the market are unlikely to have these warnings, putting patients who take them at risk of a serious unknown side effect.

When the FDA determines that a medicine requires a black-box warning, it contacts the manufacturer to request that the warning be added to the labeling. After that, the drug business submits their text to the FDA for approval. The text is printed on the package of the drug or device, as well as on the medication insert, once it has been approved by the FDA.

5. Post market monitoring

The FDA continues to monitor drug safety after it has been approved for marketing through a system called post-marketing monitoring. The Adverse Events Reporting System (AERS) was created in 1969 as an important tool for detecting adverse events in drugs. In addition to the AERS, new controlled clinical studies and reports in the literature may provide safety information.

The FDA conducts risk assessments and makes judgments about how to effectively manage new risks as new information about a drug's safety profile becomes available. New warnings, including a black box, may be added to the labeling to reflect the new safety information. A risk management program may be created if it is deemed required, and new safety signals may result in major changes in the drug's marketing status, such as limited product dispensing or, in rare situations, withdrawal from the market.

According to the authors of a review of adverse drug event surveillance, the AERS database received almost 2.3 million case reports of adverse events for nearly 6000 marketed drugs over a 33-year period from 1969 to 2002 [14].

Post-marketing Safety Surveillance and Oversight: FAERS, MedWatch, and the Sentinel System

Adverse events that were not observed during clinical trials or preapproval review may become evident after a newly approved treatment has been in use for a while. The FAERS (FDA Adverse Event Reporting System) and Sentinel One are two main systems used by the FDA to monitor post-marketing drug safety. The Sentinel System is a "active" system, whereas the FAERS is a "passive" system.

FDA Adverse Event Reporting System

The FAERS is an essential element for identifying and evaluating adverse effects. It is an electronic data repository of spontaneously submitted adverse events associated with pharmaceuticals and biological products. For the past 47 years, the Center for Drug Evaluation and Research

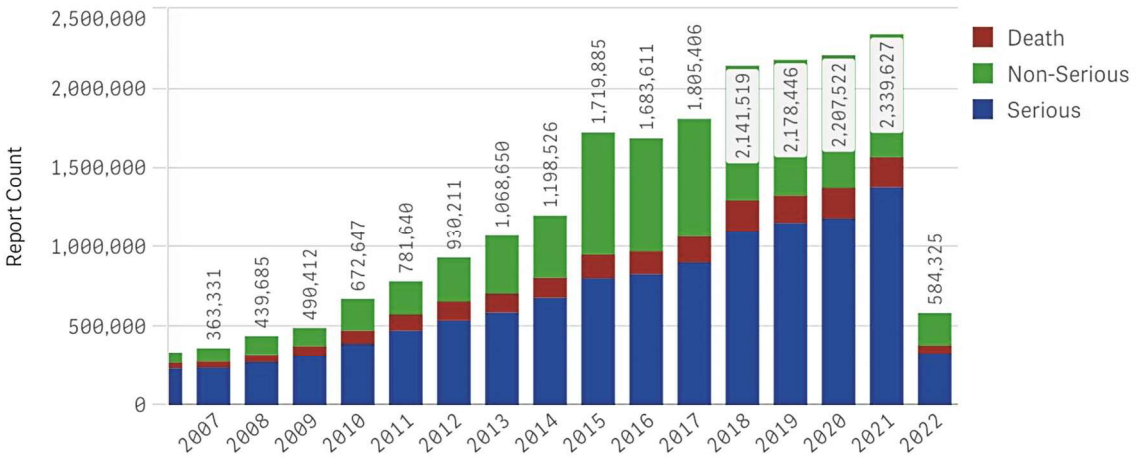

Fig. 4. Numbers of adverse events according to severity [17].

(CDER)'s post-marketing drug safety monitoring has been based on voluntary MedWatch reports from the public, health care professionals, and others. Adverse events, drug quality concerns, and medication errors seen during the use of a marketed drug product have formed the cornerstone of the CDER's post-marketing drug safety monitoring. Figure 3 illustrates the process of a drug's post-marketing reports collection.

The FAERS fills the gap between known adverse events documented in pre-approval drug testing and those seen in the general population once a medicine is approved. A thorough assessment is carried out if a significant safety problem is discovered in FAERS. Individual spontaneous reports, and also average data from the FAERS database for all marketed goods, are monitored regularly. Adverse event reports and benefit–risk evaluation reports are assessed quarterly, biannually, and annually, and full drug product safety evaluations are conducted 18 months after approval. CDER employs data mining techniques to swiftly identify the most valuable FAERS reports, and these algorithms are updated on a regular basis.

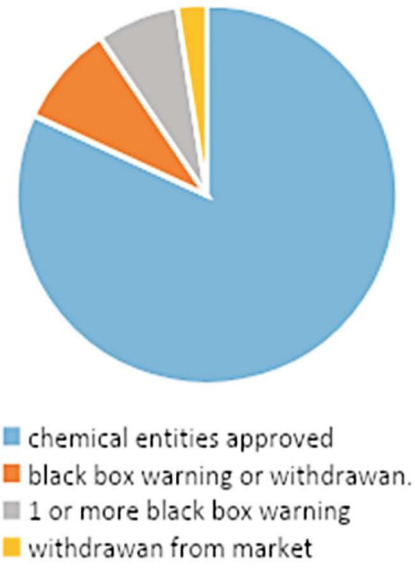

Fig. 5. Black boxed warnings and withdrawals by FDA in 1975-1999.

The graphical representation in Figure 4 depicts the number of adverse reports according to severity received and filed into the FAERS from 2007 to 2022.

The FDA gets direct submissions from the public, whereas the industry submits 15-day and non-expedited reports [12]. The 15-day reports contain significant and unexpected adverse events from spontaneous reports, as well as serious, unexpected, and considered to be reasonable AEs from the drug's clinical trials. The industry submits all other adverse event reports as non-expedited reports.

The Sentinel System: Transforming How We Monitor FDA-Regulated Products

The Sentinel System is a US-wide, integrated electronic system that monitors medication safety using common health care statistics (with care taken to protect personal health information). Sentinel routinely detects and responds to new risks associated with FDA-regulated medical devices using "big data" and large networks across various data partners, allowing for a faster evaluation of safety concerns than was previously possible [16].

New Black Box Warnings and Withdrawals

Figure 5 shows that 548 novel chemical entities were approved between 1975 and 1999, with 56 (10.2%)-obtaining a new black-box warning or being withdrawn. A total of 45 drugs (8.2%) got one or more black box warnings, with 16 (2.9%) being withdrawn from the market [18].

On 3 February 2005, the FDA issued a black-box warning noting that all antidepressants increase the risk of sui-

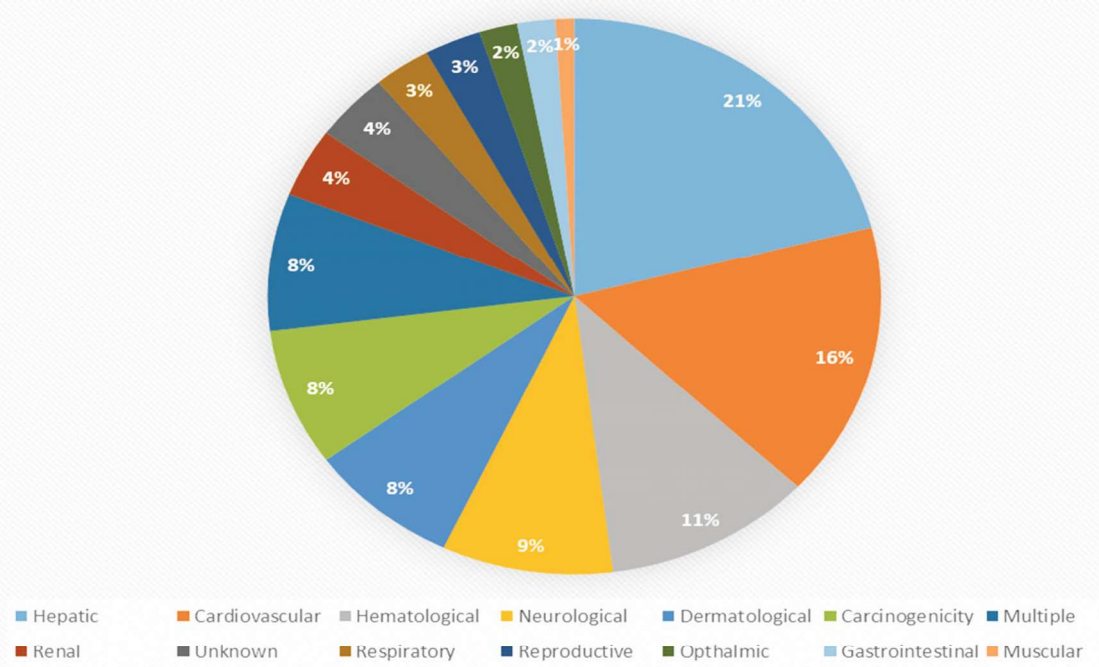

Fig. 6. Toxicity type associated with drug withdrawal [1].

cidal ideation and behavior in children and adolescents. In addition, everyone who takes such prescriptions must receive a new prescription guide from their pharmacist. Children are expected to be monitored closely by therapists and their families. Antidepressant prescriptions for children dropped dramatically immediately after this warning (Vedantam, 2005b), with unclear public health repercussions. The American Medical Association and the American Psychiatric Association have both published comments cautioning against limiting access to these treatments for those who may benefit from them [19].

TABLE 2 summarizes a few of the recent drugs for which black box warnings were issued by FDA. [20]

TABLE 2. Recent drugs with a black-box warning

No.	Drug	Reason	Year of recall
1	Macleod's losartan potassium/hydrochlorothiazide combination tablets	Detection of N-Nitrosodiethylamine impurity	2019
2	Ketorolac tromethamine injection	Lack of sterility	2019
3	Metformin hydrochloride extended-release tablets	N-Nitrosodiethylamine impurity	2022
4	Accupril (quinapril HCL) tablets 10 mg, 20 mg, 40 mg	N-Nitroso-quinapril content	2022

Post-marketing drug withdrawal

There should be more stringent monitoring and verification of fatalities and reporting of reasons for dropouts during clinical trials in the pharmacy business, as well as increased transparency in reporting adverse events and easy access to clinical trial papers from pre-marketing studies [21].

Reason for drug withdrawal

A total of 14 toxicity classes were defined based on the negative symptoms associated with medication discontinuation, one of which is represented in Figure 6, according to their withdrawal contribution. Hepatic, cardiovascular, hematological, dermatological, carcinogenic, neurological, renal, gastrointestinal, ophthalmic, muscular, reproductive, and respiratory toxicity are among them, as are "multiple toxicities," which includes compounds that cause multiple organ failure, and "unknown toxicity," which means that no specific toxic effect could be identified, despite the withdrawal being linked to a safety issue [1].

Number of withdrawn medicines in the world

National essential medications lists include the number of drugs withdrawn, as shown in Figure 7.

The countries colored gray do not have an essential medicines list that is publicly available. On the color scale, countries with fewer withdrawn drugs on their essential medicines lists are tinted lighter, whereas countries with more withdrawn medicines are colored darker [22].

TABLE 3 lists the medications in chronological order that the FDA has removed on safety grounds.

Conclusion

To date, many drugs have had to be withdrawn during their post-marketing phase. Drug development is a complex, painstaking, and time-consuming process in which it takes years to market a safe drug for use in humans. Unfortunately, some of these drugs had to be withdrawn owing to the unprecedented ADRs. Some ADRs result in a black-box warn-

TABLE 3. List of drug withdrawals, for safety reasons

No.	Drug	Year of introduction	Year of withdrawal	Reason for withdrawal
01	Metofoline [24]	1962	1965	Ocular damage
02	Diphenazine (quetidin) [24]	1962	1967	Photodermatitis
03	Ibufenac [24]	1961	1968	Hepatotoxicity
04	Fenclozic acid [24]	1969	1970	Hepatotoxicity/cholestatic jaundice
05	Pifoxime [24]	1975	1976	Neuropsychiatric
06	Alclofenac [24]	1972	1977	Vasculitis
07	Benoxaprofen [24]	1980	1982	Hepatotoxicity/cholestasis
08	Diclofenac [24]	1979	1983	Carcinogenicity
09	Antrafenine [24]	1977	1984	Acute interstitial nephritis
10	Isoxicam [24]	1983	1985	Dermatitis
11	Bucetin [23]	1968	1986	Carcinogenicity
12	Bumadizone injection [23]	1972	1986	Degenerative bone changes
13	Floctafenine [24]	1976	1987	Dermatitis
14	Fluproquazone [24]	1978	1989	Hepatotoxicity
15	Bufexamac [24]	1973	1990	Hypersusceptibility
16	Ketorolac [24]	1989	1992	GI bleeding
17	Bendazac [24]	1983	1993	Hepatotoxicity
18	Droxicam [24]	1990	1994	Hepatotoxicity/cholestatic jaundice
19	Benzydamine [24]	1967	1995	Photodermatitis
20	Flosulide [23]	1994	1996	Renal damage
21	Bromfenac tablets [24]	1997	1998	Hepatotoxicity/cholestatic jaundice
22	Nimesulide [24]	1986	1999	Hepatotoxicity/liver failure
23	Loxoprofen sodium [24]	1983	2000	Colonic ulceration
24	Alphacetylmethadol [20]	1993	2003	Cardiac arrhythmia
25	Bezitramide [20]	1961	2004	Abuse
26	Parecoxib [20]	2002	2005	Cardiorespiratory toxicity
27	Co-proxamol (PCM + dextropropoxyphene) [20]	1957	2007	Abuse
28	Ketoprofen (gel) [20]	1980	2008	Photodermatitis
29	Fentanyl hydrochloride [20]	2006	2009	Abuse
30	Celecoxib (onsenal) [25]	2003	2011	MI stroke
31	Tetrazepam [25]	1978	2013	Serious cutaneous reaction
32	Flupirtine [25]	1984	2018	Liver toxicity
33	Ingenol mebutate gel [25]	2012	2020	Increased risk of skin cancer
32	Lorcaserin [20]	2012	2020	Increased risk of cancer
33	Ranitidine [25]	1981	2020	Found to spontaneously break down into the carcinogen N-nitrosodimethylamine
34	Amifampridine 10-mg tablets [20]	2019	2021	Exceeds specification for total yeast and mold counts

GI = gastrointestinal, MI = myocardial infarction

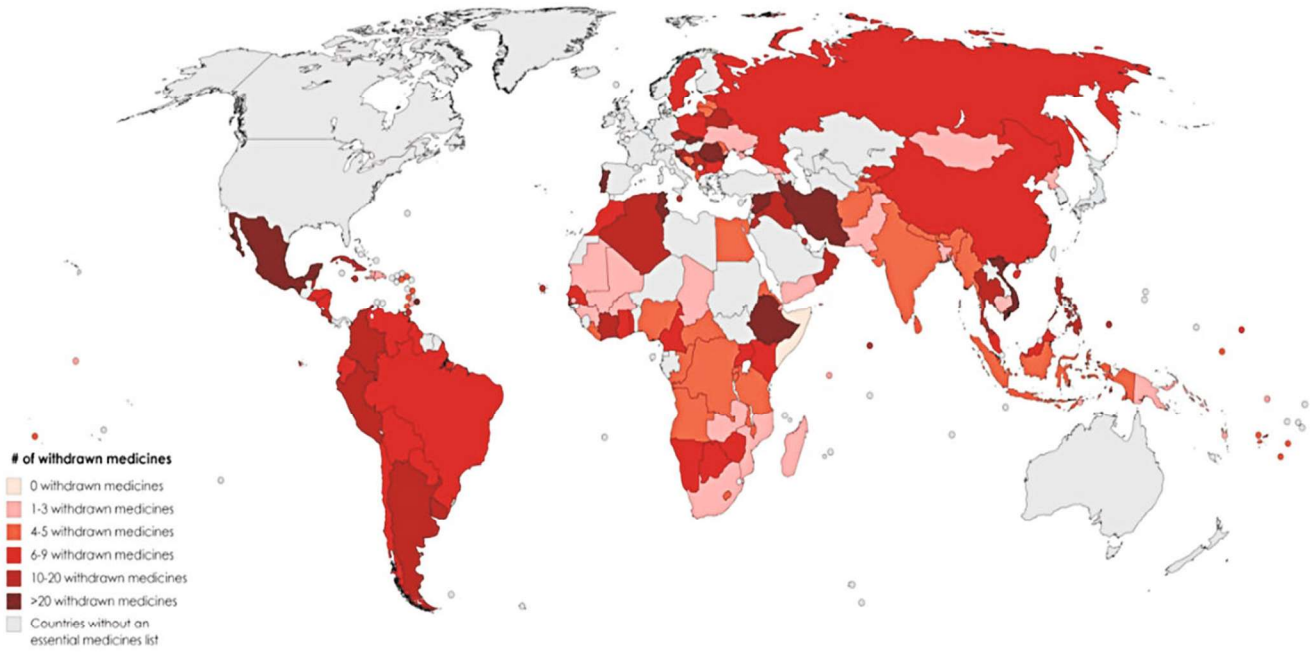

Fig. 7. Number of withdrawn medicines in the world [22].

ing. This article has appropriately reviewed such drug examples withdrawn during the post-marketing phase. The medicinal chemists have been striving and will always strive to design drugs that are selective and safe in order to avoid ADRs.

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CONFLICTS OF INTEREST STATEMENT

The authors declare that there are no conflicts of interest.

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