WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 2, 615-625. Review Article ISSN 2277– 7105

DRUGS WITHDRAWN FROM INDIAN MARKET

Vikas Vasant Pawar*[1], Darshana Patil[1] and Neha Jadhav[1]

PG Student, Dr. L H Hiranandani College of Pharmacy, Pharmacology Department, Ulhasnagar-03.

Article Received on
09 Dec. 2018,
Revised on 29 Dec. 2018,
Accepted on 19 Jan. 2019
DOI: 10.20959/wjpr20192-14165

***Corresponding Author**
Vikas Vasant Pawar
PG Student, Dr. L H Hiranandani College of Pharmacy, Pharmacology Department, Ulhasnagar-03.

ABSTRACT

Withdrawal refers to the total removal of a medicinal product from the market. Medications experience thorough testing before they are brought into the market. They are first tried in animals and afterward in individuals during clinical trails for their adequacy and also for their wellbeing. In spite everything being prevented, some unfavorable adverse effects of medications seem to appear when the medication is utilized in the all individuals after its approval. These unfavourable adverse effects are recognized though a process of regular monitoring after the drug is released into the market called Pharmacovigilance. In the event that if the unfavorable adverse effects are extreme or the dangers of utilizing the medication exceed the benefits, or if the medication is ineffective, the country may ban the medication or the medication organization may itself intentionally pull back the medication. In this review, We outlined different Drugs pulled back from Indian market and a few medications still accessibility in India, depite being prohibited or ban and the safety drug monitoring programme in India.

KEYWORDS: Medication, Ban, Withdrawn, Adverse Drug Reaction**(**ADR).

INTRODUCTION

New medications are approved when they show a great benefit to harm balance, yet the harm profile of the medicine may change after regulatory approval, when more individuals are exposed to it. Now and again, information on damages might be serious enough to warrant market withdrawal of a product. The proof utilized for making such withdrawals can be founded on anecdotal reports, observational studies, clinical trials, or systematic reviews.[1] Withdrawal implies the aggregate withdrawal of a medicinal product from the market. Medication implies any substance or mixture of substances utilized or implying to be

reasonable for use or fabricated or sold for use in - the diagnosis, treatment, mitigation, modification or prevention of disease, anomalous physical or mental state or the indications thereof in man or reestablishing, redressing or altering any substantial or psychic or organic function in man, and incorporates in any veterinary medicine.[2] Drugs experience thorough testing before they are brought into the market. They are first tried in animals and afterward in individuals during clinical trials for their adequacy and additionally security. Despite all precautions, some unfriendly impacts of medications seem just when the medication is utilized in the all general community after its approval. These adverse effects are detected though a process of regular monitoring after the drug is released into the market called Pharmacovigilance. On the off chance that the unfriendly impacts are serious or the dangers of utilizing the medication exceed the benefits, or if the medication is ineffectual, the country may ban the medication or the medication organization may itself willfully pull back the medication. A few medications may cause unfriendly impacts just when combined with specific medications. In such cases, fixed dose combination is prohibited and not the individual medications. The Purpose of the Drug Withdrawal is to adequately expel from the market products that disregard prerequisites and that may represent to a wellbeing danger to the customer/user.[3] However, a Critical number of new chemical entities (NCEs) were recalled from the market post to their regulatory approval because of different reasons extending from inefficiency to severeside-impacts to financial and regulatory concerns. Adverse Drug Reactions (ADRs) represent advertise withdrawals as well as for changes in names or presentation of new black box warning for professionally prescribed drugs.[4]

Reasons for Drug Withdrawal[2]

The withdrawal of a specific group or clumps of an product from the market might be occasioned by the accompanying:

1. Serious reports of adverse drug reactions not included in the package insert
2. Unexpected frequency of adverse reaction stated in the package insert
3. Incorrect labeling of a product
4. Incorrect formulation of a product
5. Result of ongoing stability studies (unfavorable?)

Difference Between Drug Recall & Drug Withdrawal[5]

Drug withdrawal: In some cases, FDA may need to reassess and change the medication product's endorsement choice. A choice that a medication should never again be advertised

relies on the nature and recurrence of the antagonistic occasions and how the medication's benefits and hazard offset contrasts and treatment choices. At the point when FDA perceives that the medication's benefits never again exceed its dangers, the office will request that the maker pull back the medication.

Drug Recall: A medication review is a demonstration taken by a firm to remove a medication product from the market that FDA considers to be disregarding the law. A medication might be reviewed because of components, for example, issues identified with bundling, assembling, or tainting.

Process of Drug Withdrawal[6]

At the point when a difficult issue happens in human services there is dependably an "automatic" reaction by numerous individuals to force a withdraw and therefore give a ban and complete reaction to the issue. While such reactions might be candidly fulfilling they regularly speak to answers which are "more astute than we are" and may wind up causing more damage than anything else. The exemplary case of medication prohibiting has been the adventure of thalidomide. Thalidomide, created in Germany in the mid-1950's, ended up well known on an overall premise as a sedative and rest prompting medicine. Thalidomide at first seemed, by all accounts, to be sheltered. The reality was that it was a teratogen (fit for birth absconds) related with maldevelopment of fetal furthest points. By chance, there is no basic control accessible till date constraining forbidding of medications at the same time in all nations. The Drug Technical Advisory Board (DTAB) in India is the last specialist on forcing a ban. An official board inspects the unsafe impacts of the medications and reports the outcomes to the DTAB. In the event that any medication is found to have hurtful reactions, the Government issues the boycott Officials at the Drug Controller of India (DCGI) office, be that as it may, had an alternate interpretation of the issue of restricted medications. "Screening of silly or hurtful medications is a continuous exercise and more than 79 classifications of plans have been restricted up until now. With a view to guaranteeing legitimate apportioning and objective utilization of medications, pressing has been institutionalized. Indeed, even after a medication gets advertise endorsement, security and viability is consistently inspected based on data got through pharmaco-vigilance, post-marketing observation and data got from different nations. India's commitment to the overall gathering of information as an afterthought impacts of various medications is troubling. Nations like Ireland, Switzerland and Italy with a populace of around 4 million, 33million

and 57 million individually, had submitted 25, 33, and 225 unfriendly medication responses on Nimesulide. Inspite of overall boycott medications, for example, "Nimesulide, Phenyl propanolamine, Analgin," and so forth are 27 being sold in India. At the point when an entirely beneficial medication is prohibited abroad for its unfriendly impacts, intrigue bunches in India oppose comparable activity here.

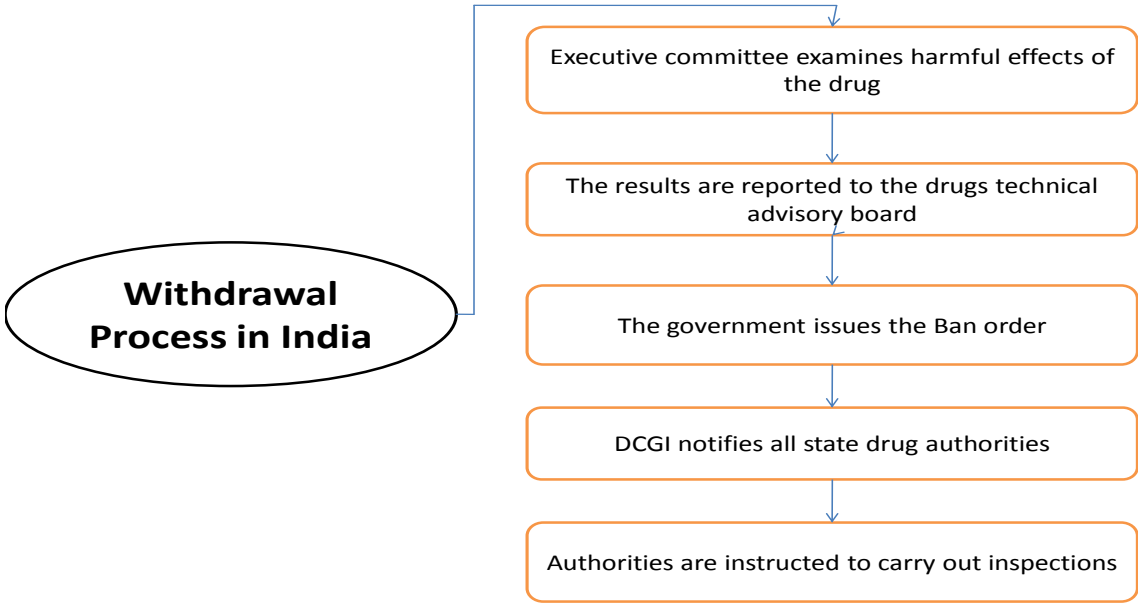

Figure 1: Process of Drug withdrawal in India.[6]

Drugs Pulled Out From Indian Market

Various single medications and in addition fixed portion mixes have been restricted for assembling, promoting and circulation in India. Some individual medications prohibited in India are referenced beneath:

Medications Used for Obesity and Weight Loss - Fenfluramine, dexfenfluramine, rimonabant, sibutramine, phenylpropanolamine. The presentation of weight reduction sedates in the Indian market gave would like to various individuals suffering from overweight and stoutness. These medications couldn't just assist individuals with a superior self-perception, yet they additionally guaranteed decrease of wellbeing outcomes of corpulence. Tragically, these medications were related with genuine side effects and must be pulled back for the accompanying reasons: Fenfluramine and dexfenfluramine affected the cardiovascular framework and were related with ailments of the heart valves, the development of fibrous tissue in the heart, and pneumonic (hypertension in the lung flow). Rimonabant was pulled

back because of its relationship with genuine mind related side effects like sadness, self-destructive propensities and seizures. Sibutramine has been prohibited since it caused cardiovascular side effects like heart assault and stroke.[7]

Non-steroidal Painkillers - Rofecoxib, Valdecoxib. Rofecoxib and valdecoxib were second era non-steroidal painkillers. They professed to give relief from discomfort without causing stomach ulcers not at all like customary painkillers like headache medicine, ibuprofen and indomethacin. Be that as it may, their utilization was overshadowed with a higher occurrence of heart assault and stroke in patients taking the medications and along these lines, they were banned.[7]

Statins - Cerivastatin was as of late pulled back from the market on account of 52 passings credited to sedate related rhabdomyolysis that lead to kidney disappointment. The hazard was observed to be higher among patients who gotten the full portion (0.8mg/day) and the individuals who got gemfibrozil associatively. Rhabdomyolysis was multiple times more typical with cerivastatin than the other five endorsed statins. We address three critical inquiries raised by this withdrawal.[8]

The List of Drugs pulled out from the market are listed in Table 1.[9]

Table 1: List of Drugs Banned in India.[9]

Sr. No	Drug name	Year of ban in India	Cause of ban
1	Amidopyrine	1983	Agranulocytosis, Aplastic anemia
2	Phenacetin	1983	Carcinogenesis, renal damage (failure)
3	Tetracycline, Oxytetracycline, Demeclocycline- liquid oral Preparations	1983	Intracranial hypertension, pericarditis. Metabolic disturbances like hypoglycaemia. Bone defects in children
4	Benzyl- Penicillin	1983	Skin lesions, pruritus
5	Practolol	1983	Oculomucocutaneous syndrome
6	Methapyrilene	1983	Liver cancer in rodents
7	Methaqualone	1983	Dependence, peripheral neuritis
8	Fenfluramine	1998	Cardiac fibrosis, pulmonary hypertension
9	Dexfenfluramine	1998	Cardiovascular side effects
10	Astemizole	2003	Cardiovascular side effects with antifungal drugs
11	Terfinadine	2003	Cardiovascular sideeffects with antifungal drugs

12	Phenformin	2003	Lactic acidosis
13	Valdecoxib	2005	Cardiovascular side-effects
14	Rimonabant	2009	Depression, Suicidal tendencies
15	Rosiglitazone	2010	Cardiovascular side-effects
16	Nimesulide in children below 12 years	2011	Liver failure
17	Cisapride	2011	Arrhythmias
18	Phenylpropanolamine	2011	Stroke
19	Sibutramine, R-sibutramne	2011	Heart attacks, Stroke
20	Gatifloxacin- Oral and Injectable	2011	Dysglycemia
21	Tegaserod	2011	Heart attacks, Stroke
22	Letrozole, for Ovulation induction	2011	Locomotor and cardiac abnormalities in the child
23	Human placental extract except topical application for wound healing and as an injection for pelvic inflammatory disease	2011	Transmission of infections, Heart attacks, Stroke
24	Dextropropoxyphene	2013	Arrhythmias
25	Pioglitazone	2013(revoked)	Bladder cancer
26	Analgin/Metamizole/Dipyrone	2014(revoked)	Agranulocytosis, Aplastic anemia

Drugs Available In Indian Market, Despite Being Banned

The Drugs which are Globally Withdrawn but still available in Indian market are listed in Table 2.[9]

Table 2: Drugs available in India, despite being banned.[9]

Sr No.	Drug name	Available as
1	Dexfenfluramine	Redux
2	Astemizole	Acemiz, Stemiz
3	Valdecoxib	Artival
4	Rimonabant	Ribafit
5	Rosiglitazone	Reglit
6	Nimesulide in children below 12 years	Nise, Nimulid
7	Cisapride	Ciza, Syspride
8	Phenylpropanolamine	Vicks Action 500
9	Sibutramine	Leptos
10	Gatifloxacin – Oral	Algat, Amgat
11	Tegaserod	Ibsinorm
12	Dextropropoxyphene (As a fixed drug Combination)	Colidex
13	Analgin/Metamizole/Dipyrone	Novalgin
14	Proglitazone	Pioz

Reasons for Availability of Banned Drugs In India[6]

1. Commercial interests of pharmaceutical organizations
2. Corruption
3. Lack of straightforwardness and responsibility
4. Regulatory bodies need implementation control

5. Due to the neediness line in India these medications are effortlessly showcased at low expenses
6. Many private professionals and doctors are ignorant about the withdrawal
7. Non-Compliance by the patient without anyone else's input recommending the medications for basic illnesses and scatters
8. Because of self medicine, quantities of hypersensitive and anaphylactic responses are happening every now and again in India. This can be averted by open mindfulness programs with respect to the status, utilize, and reactions of self solution
9. Non-accessibility of fitting medications and their staggering expense. Prescribers absence of learning and experience
10. One of the purposes behind the free accessibility of pulled back medications in the market is this correspondence hole between the DCGI and state drug controllers

The Reasons for some of the banned drugs which are still available in Indian market are listed in Table 3.[6]

Table 3: Drugs That Have Been Globally Withdrawn But Are Still Available In Indian Markets.[6]

Drug name	Category	Reason for Ban
Analgin	Analgesic	Bone marrow depression
Droperidol	Antidepressant	Irregular heartbeat
Furazolidone	Antidiarrhoel	Cancer
Nimusulide	NSAIDS	liver failure
Phenolphthalein	Laxative	Cancer
Phenylpropanolamine	cough and cold	Stroke
Oxyphenbutazone	NSAIDS	bone marrow depression
Piperazine	Antiworms	Nerve Damage
Quiniodochlor	Antidiarrheal	Damage to sight

The Need of Pharmacovigilance in India[10]

As indicated by the 2011 evaluation, India has the second most astounding populace on the planet with over 1.21 billion individuals. The pharmaceutical business in India is esteemed at 18,000 million dollars and its development is assessed at the rate of 12-14% per annum. Pharmaceutical fares are additionally becoming at 25% exacerbated yearly development rate (CAGR) consistently. The aggregate fare of pharmaceutical products adds up to 8000 million dollars, which makes India a worldwide drug store of nonexclusive medications since it is a particular element giving conventional medications, which have quality and are moderate. On a worldwide scale, India is being seen as a rising center point of clinical preliminaries,

medicate disclosure, innovative work. Following quite a while of clinical preliminaries and well ordered endorsement by medication administrative experts, a medication is presented for restoring a specific ailment. Before presentation in the market, notwithstanding a few checks in the medication disclosure and advancement process, certain medications are pulled back from the market when ADRs related with them are found. Medications may be pulled back even after they are accessible in the market for 10 years or more. Instances of such medications are rosiglitazone, rofecoxib, gatifloxacin, rimonabent and particularly nimusulide detailing utilized in the market since 12 years. A portion of the ADRs are avoidable. Unconstrained revealing by human services experts is an imperative advance for avoiding or diminishing ADRs. The ADR revealing rate in India is beneath 1% contrasted with the overall rate of 5%. Given the lower rate in India, one reason may be credited to the mindfulness about pharmacovigilance and ADR checking among the Indian medicinal services suppliers.

National Pharmacovigilance Program of India[10]

The national pharmacovigilance program (NPP) was set up by the Ministry of Health and Family Welfare in New Delhi in 2010 as a way to accumulate ADR reports all through the country. The NPP contains a national planning focus that gets ADR data from individual pharmacovigilance focuses about the reason, source and the work force associated with an antagonistic medication occasion by means of a vigiflow programming interface worked by Uppsala Monitoring Center. The NPP has created and extended through fives periods of advancement since its introduction in 2010. In its introduction stage from 2010-2011, 40 restorative schools were set up as pharmacovigilance focuses and work force were prepared in these pharmacovigilance focuses. In the extension and combination stage from 2011-2012, extra 60 therapeutic schools were selected as a component of NPP and holes in preparing the staff working in the pharmacovigilance focuses were recognized. In the development and support stage from 2012-2013, another 100 therapeutic schools were enlisted as a major aspect of NPP. In the development and improvement stage to be actualized later on from 2013-2014, the NPP wants to enlist an extra of 100 restorative schools. The NPP will likewise set up the Center of brilliance for pharmacovigilance in Asia Pacific Region as a major aspect of the perfection stage to be actualized in 2014-2015. All through the five stages, the NPP has and will arrange open mindfulness workshops for advancing medication wellbeing and viability.

Sub-Committee To Monitor Banned Drugs In India[10]

Every nation has its very own association that screens its individual course of prohibited medications. In India, preceding medication advertising, its wellbeing and adequacy is found out as per the Schedule Y of Drugs and Cosmetics Act. Indeed, even post-retail endorsement, the security and viability of the medication is persistently inspected based on data assembled by means of Pharmocovigilance, Post-Marketing Surveillance and data detailed from different nations. So as to analyze such data, the Drugs Technical Advisory Board (DTAB) under Drugs and Cosmetics Act has established a sub-council, comprising of specialists regarding the matter who inspect the data got from the sources referenced above and accept a last view with respect to whether to disallow the make, deal and conveyance of medications or to limit its utilization and in like manner prescribe the Government to make reasonable revisions under Section 26 An of the Drugs and Cosmetics Act which enables the Central Government to deny the make, deal or dispersion of such medication or makeup.

The Role of Pharmacist In Drug Safety[10]

A multifaceted methodology is required for wellbeing of prescription direction in the Indian market. A helpful initial step is to build up straightforwardness, which isn't evident directly. The drug specialist can assume a vital job in medication wellbeing. Thus every state medicate control officer ought to entirely submit to the Drug and Cosmetic Act 1940, which commands each drug store to have a drug specialist consistently amid business hours. Drug specialist can instruct associate drug specialists and in addition patients visiting the drug store by composing marks in simple and reasonable dialect, quiet guiding, giving handouts and stick publications about certain ADRs identified with the got prescriptions and counsel to report ADRs to drug specialists or other human services experts.

Continued Education (CE) is critical for drug specialists for refreshing and reviving their insight about ongoing headways and changes in pharmaceuticals. CE likewise helps in teaching drug specialists about the NPP including how to report and whom to report ADRs in their training. The administration of India can likewise teach all inclusive community about discovery alerts through a media. By and by, just a single Pharmacy College associated with the J.S.S. Medicinal College and part of J.S.S. College, Mysore is associated with the NPP, however already even network drug stores situated in the province of Goa and numerous drug store schools situated in south India went about as fringe pharmacovigilance focuses. Sadly, the NPP concentrates just on restorative schools and not on other medicinal services offices.

Drug specialists and medical attendants are a basic piece of enhancing mindfulness about pharmacovigilance in India. Their endeavors add to the smooth running of the NPP and support of avant-garde documentation henceforth they ought to be given due acknowledgment and considered a fundamental piece of NPP.

The pharmacovigilance system in India is extremely poor and the expanded remaining task at hand on doctors, medical attendants and drug specialists does not convey to their notice the vast majority of the ADRs happening by and by. Drug specialists should apportion precise prescriptions and they have prime information on meds. Sadly in India the capability for a drug specialist to work in a drug store is a confirmation (certificate in drug store a multi year examine in addition to 500 hour down to earth preparing in clinic), and not a baccalaureate degree in drug store.

In addition the instructive educational programs in India for drug specialist is more centered around industry instead of on network drug store. In any case, things are changing and courses dependent on drug store practice are being educated in numerous drug store schools in South India as a major aspect of projects, for example, Pharm. D. what's more, M. Pharm. drug store practice. On the off chance that the present age of drug specialists get engaged with the NPP, we can expect an expansion later on location of ADRs being accounted for back to the concerned experts, which thusly will assist the administration with taking the required activity at the most punctual.

CONCLUSIONS

In the event that all medicinal services proficient including doctors, attendants, drug specialist and others including the patient report all ADRs then administrative expert can make a move as quickly as time permits, and medications which are restricted worldwide might be not accessible in India as well. The significance of empowering doctors, drug specialists, other social insurance experts, and patients to keep on announcing genuine presumed unfavorable medication responses, regardless of whether obscure or known, to makers and their neighborhood administrative offices can't be over accentuated. Medication improvement is winding up progressively troublesome. Proceeded with steady loss of conceivably valuable medications in view of genuine undesirable impacts won't help. Cautious premarketing screening ought to lessen the issue yet may likewise diminish the quantity of possibly valuable medications accessible for full advancement and ensuing permitting. Better hazard

the executives techniques are expected to deal with issues when they emerge, by means other than renouncement of licenses.

REFERENCES

1. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of analgesic medications because of adverse drug reactions: a systematic review. Expert opinion on drug safety, 2018 Jan 2; 17(1): 63-72.
2. Guidelines for Product Recall and Product Withdrawal First Edition, https://www.medscape.com/resource/clinical-trials/glossary
3. Siramshetty VB, Nickel J, Omieczynski C, Gohlke BO, Drwal MN, Preissner R. WITHDRAWN—a resource for withdrawn and discontinued drugs. Nucleic acids research, 2015 Nov 8; 44(D1): D1080-6.
4. Drug recall: An incubus for pharmaceutical companies and most serious drug recall of history Upendra Nagaich, Divya Sadhna1.
5. Shaji J, Lodha S. Regulatory status of banned drugs in India. Indian Journal of Pharmaceutical Education and Research, 2010 Jan 1; 44(1): 86-94.
6. https://www.quora.com/What-is-the-legal-procedure-to-ban-a-pharmaceutical-drug-in-India.
7. Furberg CD, Pitt B. Withdrawal of cerivastatin from the world market. Trials., 2001 Oct; 2(5): 205.
8. Chhaya MU. Banned, for real?. INDIAN JOURNAL OF APPLIED RESEARCH, 2018 Feb 13; 7(5).
9. Ahmad A, Patel I, Sanyal S, Balkrishnan R, Mohanta GP. A study on drug safety monitoring program in India. Indian journal of pharmaceutical sciences, 2014 Sep; 76(5): 379.