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The Persistence of Risk: Analysing Banned Drugs in India's Healthcare System

Abstract: The availability of drugs banned in other countries due to safety, efficacy, or ethical concerns but still marketed in India is a significant public health issue. Various factors contribute to this disparity, including regulatory gaps, differing standards for drug approval, and inadequate post-marketing surveillance. Drugs like Ranitidine, Pioglitazone, and certain fixed-dose combinations (FDCs) have faced scrutiny globally, with bans or restrictions in place in nations like the United States, European Union, and Japan due to severe adverse effects, including carcinogenicity, organ toxicity, or lack of therapeutic efficacy.

India's drug regulatory framework, overseen by the Central Drugs Standard Control Organization (CDSCO), has been criticized for slower updates to regulations, weak enforcement, and influence from pharmaceutical companies. Efforts have been made in recent years to address this gap, such as the 2018 ban on several irrational FDCs and initiatives to align Indian pharmacovigilance with global standards.

This abstract highlights the need for strengthened regulatory mechanisms, better alignment with international norms, and robust pharmacovigilance systems to ensure the safety and efficacy of drugs available in India. Policymakers must prioritize harmonizing India's drug approval processes with international best practices to protect public health and restore confidence in the regulatory system.

1. Introduction

The presence of drugs banned in other countries but still circulating in India's healthcare system presents a critical issue for public health. Drugs are typically banned due to their association with severe side effects, long-term health risks, or the availability of safer alternatives. However, in India, several such drugs continue to be prescribed and sold, raising concerns about regulatory oversight and patient safety. This review aims to examine

the factors contributing to the persistence of these banned drugs in India's healthcare system and the associated risks. The prevalence of diseases is constantly increasing in the present-day scenario, and the major concern of drug manufacturers, doctors, and other healthcare professionals is to guarantee the quality of drugs with determined therapeutic advantages and low adverse side effects.[1-3] Unanticipated adverse side effects, superfluous toxic effects, accessibility for safer substitutes, detrimental interactions, irrational combinations, and the risk of management failures are the key factors that decide whether to use or ban a drug. When drugs are found to be unsafe in post-marketing surveillance conducted, then developed countries immediately impose a ban through regulatory bodies on the manufacture and sale of a drug.[4]

However, in India, imposing a ban on a drug is a lengthy and time-consuming procedure which is the key reason for the persistence of banned drugs in the market even though the drug is banned in other countries.[2,4] Another major reason for the availability of banned drugs is that adequate ADR information about these drugs has not been conveyed.[5] The present review elaborately discusses the drugs banned in other countries still available in Indian markets and the reason for their persistence and compares the drug safety monitoring systems in developed countries and affords allegations for improving a system in India that can warrant the safety and efficacy of drugs.[1]

banned drugs- banned drugs are drugs that not allowed to intake because they could artificially improve their performance and shows various adverse effects more than therapeutic effects. Whose production or use is prohibited or strictly controlled via prescription.[2]

India has become a hub for the availability and usage of banned or harmful medicines such as Nimesulide, D'cold, Novalgin, Lomofen, and Rofecoxib, among others. The decision to ban a drug is based on the risk versus benefit ratio evaluated through post- marketing surveillance and the Adverse Drug Reaction Reporting System. Pharmaceutical negligence among doctors can lead to hazardous effects on the general health of a patient. It is important for the government to spread information on drugsideeffects. The prescribing of drugs is an essential practice for medical professionals. In promoting a healthy lifestyle, the prevention of diseases is important, but equally important is treatment of such diseases with safe drugs. Every drug has some side effects, but with the correct dosage, it can be avoided. Banned drugs have more adverse/side effects. Drugs that are found unsafe in post-marketing surveillance are banned by regulatory authorities. The Drug Controller General of India (DCGI) is the highest authority in India to approve or ban a drug. Despite this, banned drugs are still available in developing countries such as India due to a lack of law enforcement, physician awareness, and drug control authorities failing to inform hospitals of the status of medicine. India is a major hub for banned drugs.[3]

The numbers of single drugs as well as fixed dose combinations drugs are banned in other countries but they have manufacturing, marketing and distribution in India. Over the counter availability of banned drugs sufficient adverse drug reactions data about these drugs have not been reported. The adverse effect of drugs is detected by regular monitoring after the drug released called pharmacovigilance. The Indian regulatory authority monitoring the new drug in market before pre-clinical study and permit to sold in market. The banned dugs prescribed over the counter the responsible as unawareness of physicians and patients, poverty, self-medication, carelessness of regulatory authorities, non availability of appropriate drugs, high cost, and communication. The Government of India is in the process of developing a regulatory regime designed to ensure the quality, safety and performance of medical devices.[4]

Medical tourism and pharmaceutical boom are remarkable achievements of India over other countries due to hospitality, low cost quality treatment plans, easy research methodologies & less medico legal implications. Despite such major global

responsibility, India is becoming a hub for the availability and usage of banned medicines. The proliferation of banned and harmful drugs in India is a serious problem for the health of people and there is an urgent need to curb it. A drug is banned on the basis of risk versus benefit ratio which is evaluated through post marketing surveillance and adverse drug reaction reporting systems. The medicines which have been labeled as silent killers overseas are making their space in India, indicating lack of knowledge among doctors and inefficient government policies. Drugs play a crucial role in saving lives, restoring health, preventing diseases and epidemics. When

drug itself is harmful, it poses additive danger to the patient. Availability of such medicines over the counter is a grave problem. Medical profession is getting defamed and crippled in India because of various factors like self medication, unethical drug promotion, medical commercialization and unawareness among doctors. Until such issues are not sorted out the existing situation would prevail.[5]

2. Background and Literature Review:

India's drug regulation system operates under the Central Drugs Standard Control Organization (CDSCO), which is responsible for approving and monitoring pharmaceuticals. However, disparities between Indian and international drug regulations highlight significant gaps. While many countries adopt strict policies based on new scientific evidence, India's response to banning harmful drugs has been slower. For instance, drugs like Analgin Pioglitazone were banned or restricted in countries like the US and UK due to severe side effects, but they continued to be used in India for extended periods.

This disparity points to regulatory weaknesses, such as insufficient pharmacovigilance systems, a slower response to adverse drug reactions, and sometimes economic pressures that affect decisions. As a result, drugs proven harmful or ineffective in other regions still find a market in India.

Nimesulide is a non-steroidal anti-inflammatory drug with analgesic and antipyretic properties which was launched in Italy as Aulin® in 1985. Huge concerns were raised regarding this drug as its users are at a high risk for developing a serious ADR called Drug-Induced liver Injury which may lead to liver failure. The goal of this study was to sheds light on nimesulide which is present illegally in private pharmacies and to the harm that it may pose on public health; in order to draw the attention of the responsible authorities to the danger of its availability in our market. A survey of 65 pharmacies in Tripoli was conducted to identify the availability of nimesulide in these pharmacies. The knowledge of its different dosage forms, strength, brands available, pattern of prescribing, and ADRs among pharmacists and coworkers were all collected. 100 % response was obtained as 65 pharmacy personnel answered the questionnaire. We found out that this medicine is available in all of them. The response to the questionnaire is illustrated in figures from1 to 4. Nimesulide dispensing pattern was shown to be almost always through

atients' request. In conclusion, the uncontrolled presence of this medicine may pose a public health risk, therefore a request for its ban from Libyan market should be seriously considered(Amal Y Benkorah, Manal Hadood, Aisha Rafaei, Ghazi
Benkura*Libyan Journal of Medical Research 14 (1), 70-77, 2020)*

A Number of drug that are banned in abroad are freely available in the Indian market. The most pitiable feature is that use of these drugs are regularly causing long term implication for our physical health. Some of the common ones that are easily available and people use frequently without doctor's prescription are D-cold, Nimesulide and Analgin. These are use as pain killer but latest research shows that long term use of such medicines can affect human health in various ways by damaging liver, causing irregular heartbeats, depression, blood pressure fluctuations etc. This is the prime reason that most of European countries have disqualified and banned the manufacturing and consumption of these drugs. It has been recently pointed out that Indian drug regulatory authorities have refused to ban sale of 11 drug, including
Furazolidone, Phenypropanolamine, Cisapride and Nimuselide, apart from over 80 drug combinations that are prohibited in other countries IPA have made various regulation and guideline for the control of these drug, but still they are in use because of lack of awareness in people.*(Priya Diwedi Critical review in pharmaceutical sciences 1 (3), 1- 2, 2012)*

The numbers of single drugs as well as fixed dose combinations drugs are banned in other countries but they have manufacturing, marketing and distribution in India. Over the counter availability of banned drugs sufficient adverse drug reactions data about these drugs have not been reported. The adverse effect of drugs is detected by regular monitoring after the drug released called pharmacovigilance. The Indian regulatory authority monitoring

the new drug in market before pre-clinical study and permit to sold in market. The banned dugs prescribed over the counter the responsible as unawareness of physicians and patients, poverty, self-medication, carelessness of regulatory authorities, non availability of appropriate drugs, high cost, and communication. The Government of India is in the process of developing a regulatory regime designed to ensure the quality, safety and performance of medical devices.(Manohar D Kengar, Ganesh B Jagtap, Akshata S Gavade, Manojkumar

M Nitalikar *Asian Journal of Research in Pharmaceutical Science 8 (4), 258-260, 2018)*

3. Case Studies of Banned Drugs in India

3.1 Propyphenazone

1. Introduction/Background of the Drug

- **Generic Name:** paracetamol + propyphenazone + caffeine. The brand name for this combination is Saridon
- **Drug Classification:** pyrazolone derivative
- **Approval Date in India:** The Central Drugs Standard Control Organization (CDSCO) approved phenylbutazone 125 mg + propyphenazone 125 mg tablets in February 1980

2. Rationale for Use

- **Intended Benefits:**

Saridon is an analgesic commonly used for headaches, common cold, and menstrual cramps. It is an over-the-counter medication that provides instant relief to patients

- **Common Prescriptions:**

List of the most common conditions for which doctors prescribed this drug in India.

3. Issues/Adverse Effects Leading to the Ban

- **Adverse Reactions:** Adverse effects are uncommon and include skin rashes, pruritus (itching), erythema, angioedema, breathing problems such as dyspnea and asthma, anaphylaxis (serious allergic reactions), and decrease in the number of blood cells such as thrombocytopenia, leucopenia, agranulocytosis, and pancytopenia.The latter type of side effect can be severe.(Jentzsch A, ed. (1998). Austria-Codex)

- **Clinical Studies:** Propyphenazone (1,2–dihydro-1,5-dimethyl-4-(1methylethyl)- 2-phenyl-3H-pyrazol-3-one; PP) is a nonsteroidal antiinflammatory drug frequently used as mild analgesic medicament. It belongs to the chemical group of pyrazolones. Severe adverse reactions to PP are frequent and have generally been regarded as pseudoallergic or intolerance reactions. Presently, there are no useful in vitro test systems available for the detection of antibodies directed against analgesic drugs. Objective: The purpose of this study was to unequivocally demonstrate that IgE-mediated Type I allergy is the main mechanism leading to immediate-type adverse reactions to the analgesic drug PP. Methods: We investigated 53 young adult patients with adverse reactions to PP. All patients developed symptoms suggestive of IgEmediated anaphylaxis within 30 minutes after intake of a painkiller containing PP. Patients were subjected to skin tests (prick test and intracutaneous test). In addition, a novel ELISA system was developed to prove the existence of specific IgE antibodies in patients' sera. Results: In 44 of 53 (83%) patients, skin tests showed typical wheal and flare reactions. Significant amounts of PPspecific serum IgE was detected in 31 of 53 (58%) of the serum samples. Moreover, in 7 of 9 patients with skin test negative results, PP-specific IgE could be detected. The assay was

PP-specific because only PP, but no other pyrazolone derivative (antipyrine, aminophenazone, or metamizol), was able to inhibit IgE-binding in the system. Conclusion: Propyphenazone is a sensitizing agent in susceptible individuals and can elicit IgE-mediated anaphylaxis. By using skin tests and our ELISA system we were able to confirm Type I allergy in

51 of 53 (96%) patients in this study*(.Martin Himly PhD[a], Beatrice Jahn-*

Schmid PhD[c], Klaus Pittertschatscher PhD[b], Barbara Bohle PhD[c], Karl Grubmayr PhD[d], Fátima Ferreira PhD[a], Herwig Ebner MD[e], Christof Ebner)

Reports by Regulatory Bodies:

4. Official Reasons for the Ban

- Reasoning by Indian Regulatory Authorities:

Propyphenazone is also understood to cause serious side-effects to the bone marrow, Dr Anurag Bhargava, professor, department of medicine, Yenepoya Medical College, Mangaluru had told The WEEK after the drug ban in September 2018.

According to Bhargava, the original Saridon, manufactured by Roche pharmaceuticals, contained phenacetin. This ingredient, he says, was dropped later because it was found to be carcinogenic, and with side-effects to the kidney. “The current ingredient in Saridon, propyphenazone, also figures on the WHO's 'Consolidated List of Products Whose Consumption and/or sale have been banned, withdrawn, severely restricted or not approved by governments,” he said. (*Namita Kohli)*

WHO comment: “Propyphenazone, a pyrazolone derivative With antiinflammatory, analgesic and antipyretic activity, was Introduced in 1951 for the treatment of rheumatic disorders. As it is Structurally related to aminophenazone it has been associated with Severe blood dyscrasias. However, it cannot be transformed into Potentially carcinogenic nitrosamines and has therefore been widely Used as a replacement drug for aminophenazone. In certain Countries, products containing propyphenazone have now been Restricted in their indications, whereas in others they are still Available, sometimes as over-the-counter preparations.”

- Sri Lanka
- Malaysia
- Thailand
- Turkey: Banned for production and sale in January 1986

Because of severe adverse reactions India

In September 2018, Saridon, along with 327 other FDCs, was banned by the Central Drugs Standard Control Organisation.[11]Later, in the same month, based on extensive safety data submitted by Piramal, the Supreme Court of India stayed the centre's decision and allowed the sale of Saridon(Sinha B (17 September 2018))

Date of Ban: September 2018

Case study : Pyrazolone intoxication accounts for most (52 percent) mild analgesic poisonings in West Germany. Severe and fatal intoxication with pyrazolones is, however, rare. In the German literature, only 50 cases have been described in the past 62 years; 80 to 90 percent of these were caused by aminopyrine, which was withdrawn from the West German market in 1978 and replaced by propyphenazone. Up to now, no fatal poisoning with propyphenazone has been reported. However, the signs and symptoms of severe intoxication are similar for both propyphenazone and aminopyrine. The acute toxicity of dipyrone is slightly lower than that of propyphenazone, whereas phenylbutazone and oxyphenbutazone clearly cause less severe reactions. Characteristic symptoms include impaired consciousness progressing to coma, and convulsions. In addition, arrythmia and cardiogenic

shock may occur. Severe aminopyrine intoxication may also be complicated by sudden apnea. Liver damage may develop after a latent period of about 24 hours, especially afterphenylbutazone and oxyphenbutazone poisoning. Therapy involves supportive measures as well as gastric emptying by emesis or lavage, installation of medical charcoal, and induction of diarrhea or gut lavage. Although exact clinicotoxicologic data on hemoperfusion are not available as yet, distribution volumes, plasma half-lives, and endogenous plasma clearances as well as results of in vitro trials all suggest the efficacy of this procedure. Hemoperfusion with uncoated amberlite XAD- 4 resin is, therefore, recommended for patients with severe pyrazolone intoxication.

3.2 Nimesulide

- **Introduction**

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) Having analgesic and antipyretic effects that are primarily COX-2 Selective. This medication is used to relieve pain. It relieves mild to Moderate pain caused by menstrual cramps and osteoarthritis in Adults and teenagers over the age of 12. Nimesulide reduces the Intensity of pain signals transmitted to the brain and also prevents The synthesis of prostaglandins (substances that relay pain and heat Signals to the brain)

Generic name: nimesulide

Drug classification: Nimesulide is classified as a cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drug (NSAID)

Apprual date in india: Nimesulide was approved in India for transdermal gel and suppository forms between 1991 and 2000

2. **Rationale for Use**

When there are joint problems, such as arthritis, Nimesulide is used to reduce pain, swelling, and inflammation. Moreover, it eases pain from surgery, dental pain, mild sprains and strains, and ear, nose, and throat pain. In addition, it is used to treat osteoarthritis and menstrual cramps that are extremely painful.

Moreover, it alleviates mild to severe pain brought on by muscle and joint sprains and strains. But children under 12 shouldn't use Nimesulide, as it carries a serious risk of liver damage.

- **Intended benefits:**

In countries where nimesulide is approved for human use, it may be used to treat conditions such as acute pain, osteoarthritis and primary dysmenorrhea (menstrual pain) in adolescents and adults above 12 years old. In some countries, this medicine may only be approved for veterinary use.(*Medically reviewed by Leigh Ann Anderson, PharmD. Last updated on Nov 21, 2022.*)

- **Common Prescriptions**: Current indications vary by country, but are generally limited to mild-to-moderate acute pain for which the recommended dose in adults is 100 mg twice daily for no more than 15 days. Chronic therapy is not generally recommended, and nimesulide is considered contraindicated in children.

3. Issues/Adverse Effects Leading to the Ban

- **Advarce reaction**: side effects can include headache, dizziness, somnolence, gastrointestinal upset, nausea, abdominal discomfort, diarrhea, peripheral edema and hypersensitivity reactions.

- **Clinical Studies**: The pharmacokinetic profile and efficacy of nimesulide were assessed in 2 separate studies that recruited children with hypoglycaemia or upper respiratory tract infection and fever, respectively.

A single dose of nimesulide 50mg (granules) administered orally to 14 hypoglycaemic children was rapidly absorbed. A mean maximum nimesulide plasma concentration of 3.5 mg/L was achieved within 2 hours of administration, which subsequently declined over the following 12 hours. Nimesulide was metabolised to its principal hydroxy metabolite, which was detectable in samples obtained 0.5 hours after giving the parent drug. Levels of this metabolite steadily increased, surpassing those of intact nimesulide at the 9-hour sampling point.

In a randomised nonblind clinical investigation, 100 hospitalised children with acute upper respiratory infections and fever received nimesulide oral suspension (5 mg/kg/day) or paracetamol (26 mg/kg/day) for 3 to 9 days. The antipyretic and anti-inflammatory effects of nimesulide were superior to those observed with paracetamol ($p < 0.01$) and both drugs
were equally well tolerated.*(* **AG Ugazio, S Guarnaccia, M Berardi, I Renzetti - Drugs, 1993 – Springer)**

The anti-inflammatory, analgesic and antipyretic activities of nimesulide, a non-steroidal anti-inflammatory drug (NSAID) of the sulfonanilide class, have been demonstrated in a number of experimental models and in numerous clinical trials. Nimesulide has exhibited potency similar to or greater than that of indomethacin, diclofenac, piroxicam and ibuprofen in standard animal models of inflammation such as carrageenin-induced rat paw oedema and inflammation, ultraviolet light-induced erythema in guinea-pigs and adjuvant arthritis in rats. The analgesic potency of nimesulide was similar to that of ibuprofen and less than that of indomethacin in an acetic acid writhing test in rats, and acetic acid and acetylcholine writhing tests in mice. Nimesulide has shown superior antipyretic potency to indomethacin, ibuprofen, aspirin and paracetamol (acetaminophen) in rats with yeast-induced fever.

(Rick Davis, Rex N Brogden)

4. Official Reasons for the Ban

- **Reasoning by Indian Regulatory Authorities:**

Ban of Nimesulid The Nimesulide induced toxicity and its severity lead to liver transplantation sometimes death. The cases reported throughout the world made the drug to get ban in many countries completely, the regulatory bodies involved in ban of the drug were given in table 1. But in some countries like India the drug is partially banned and also available as over the counter medication for adult use. No pharmacist warns the patient about possible interactions and drug induced toxicities of over the counter medications, as if they are bothered only about their sales and business. The inspectors also not bothered to enquire about over the counter medication records. The Indian government announced ban on the drug in 2011 for pediatric usage where as the drug is available for adult use in present day Indian market. The general procedure involved in ban of a drug in India (*C. Muralikrishna Goud*, Syeda Mariya Ghazanfar)*

- The continuing use of nimesulide for Indian children is shocking.[1] Numerous studies have established the life threatening hepatotoxic effects of nimesulide.[2,3]

Nimesulide is not used in the United States, and many European countries have also banned the drug because of its unacceptable rate of serious adverse reactions.

Although some studies have indicated that nimesulide may be chosen for osteoarthritis in selected patients with associated gastric problems, other nonsteroidal anti-inflammatory drugs such as acetaminophen (paracetamol) are far better choices as antipyretics or analgesics, especially for children.[4] No rationale exists for selecting nimesulide as the first drug of choice for fever or pain. Published studies from India indicate rampant abuse of nimesulide.[5] At least 12 paediatric preparations of nimesulide are available in India, which affirms the widespread use of the drug in children.*(Kunal Saha, assistant professor)*

Date of ban : On February 12, 2011, Indian Express reported that the Union Ministry of Health and Family Welfare finally had decided to suspend the pediatric use of the analgesic, Nimesulide suspension. From 10 March

2011 onward Nimesulide formulations are not indicated for human use in children below 12 years of age.

Case study : Case from India

• A 6 year old boy.who was suffering from fever for 4 days for which he was treated with Nimesulide (without prescription) for 4 days before coming to doctor. On examination, patient was found with jaundice and haematuria. *(C. Muralikrishna Goud*, Syeda Mariya Ghazanfar)*

• A 58 year old woman began to feel unwell approximately 10 days after starting nimesulide for chronic back pain. She was seen and found to have mild elevations in serum enzymes (Table). Nimesulide was continued, but she developed further symptoms including nausea and it was stopped. Two weeks later, she noted dark urine and jaundice and shortly thereafter she was admitted to the hospital because of worsening symptoms. She had no history of liver disease, alcohol abuse or risk factors for viral hepatitis. She had taken nimesulide for short periods in the past. Her other medications included birth control pills which she had taken for 6 years and sertraline which she had taken for 11 months. On admission, she was acutely ill with jaundice and confusion. Laboratory results showed a total bilirubin of 16.9 mg/dL, ALT 1046 U/L, AST 386 U/L, alkaline phosphatase 114 U/L, GGT 112 U/L, albumin 2.8 g/dL and INR greater than 12. Tests for hepatitis A, B, C, EBV and CMV were negative. She had low titers of ANA (1:25). Abdominal ultrasound showed normal liver, spleen and biliary system and a small amount of ascites. She rapidly deteriorated and required assisted ventilation. She developed progressive hepatic failure and underwent emergency liver transplantation within 3 days of admission, but had primary graft nonfunction, multiorgan failure and died within a day of the surgery. Autopsy revealed massivehepatic necrosis.(*McCormick PA, Kennedy F, Curry M, et al. COX-2 inhibition and fulminant hepatic failure Lancet 1999; 353 (9146))*

3.3 Pioglitazone

1 Introduction : Pioglitazone is an orally administered insulin sensitising thiazolidinedione agent that has been developed for the treatment of type 2 diabetes mellitus.

* Pioglitazone activates the nuclear peroxisome proliferator activated receptor-γ (PPAR- γ), which leads to the increased transcription of various proteins regulating glucose and lipid metabolism. These proteins amplify the post-receptor actions of insulin in the liver and peripheral tissues, which leads to improved glycaemic control with no increase in the endogenous secretion of insulin.

* In placebo-controlled clinical trials, monotherapy with pioglitazone 15 to 45 mg/day has been shown to decrease blood glycosylated haemoglobin (HbA_{1c}) levels in patients with type 2 diabetes mellitus.

* The addition of pioglitazone 30 mg/day to preexisting therapy with metformin, or of pioglitazone 15 or 30 mg/day to sulphonylurea, insulin or voglibose therapy, has been shown to decrease HbA_{1c} and fasting blood glucose levels significantly in patients with poorly controlled type 2 diabetes mellitus.

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* Pioglitazone has also been associated with improvements in serum lipid profiles in randomised placebo-controlled clinical studies.

* The drug has been well tolerated by adult patients of all ages in clinical studies. Oedema has been reported with monotherapy, and pooled data have shown hypoglycaemia in 2 to 15% of patients after the addition of pioglitazone to sulphonylurea or insulin treatment. There have been no reports of hepatotoxicity. (*Peter S Gillies, Christopher J Dunn)*

Generic name : Actos is a brand-name medication. It's also currently available in generic form, which is called pioglitazone. A generic drug is an exact copy of the active drug in a brand-name medication. **Drug classification:** thiazolidinedione (TZD) drug **approved in India on:** October 17, 2000

2.Rationale for Use : Pioglitazone promotes insulin sensitivity in the liver, muscle, and adipose tissue via increased insulin receptor signaling, pAMPK and GLUT4 expression and can increase glucose uptake by 30–50% within these organs(Nicholas J. Hunt, ... Victoria C. Cogger, in Advanced Drug Delivery Reviews, 2022)

Intended benefits :

Clinical studies: Type II-diabetes mellitus (T2DM) is a chronic metabolic disorder which is treated with oral hypoglycaemic agents including pioglitazone. The present work is aimed to collect a brief profile of pioglitazone, belonging to the thiazolidinedione class and controversies surrounding its use. Pioglitazone which was marketed in 1999 acts on the nuclear peroxisome proliferator-activated receptor γ PPAR-γ in adipose tissue, skeletal muscles and liver. Pioglitazone is safe, potent, insulin sensitizing gene activator and regulate blood sugar level when administered orally alone or combination with sulphonyl ureas or metformin. India is one of the leading T2DM patients country and most patients are using pioglitazone because of its efficacy and economy. Even though it is a safe drug for diabetics, it was observed that it causes adverse effects like hepatotoxicity, cardiac failure, osteoporosis and urinary bladder cancer and hence pioglitazone was suspended in India in June 2013 for

a brief duration by the Indian government. There are over 30 lakh people in India using this drug and there is no strong evidence to show that the drug has serious life threatening side effects in patients in India and also using Pioglitazone is less expensive than other drugs. By considering the safety, efficacy, potency and economy, health ministry of India revoked the earlier suspension on the diabetic patients and has allowed the manufacture and prescription of Pioglitazone and its formulation with several conditions. Hence, there is a lot of debate about benefit to risk ratio of this drug. Our study presenting brief information about pioglitazone and its controversies for diabetic mellitus in India.

3.4 Dextropropoxyphene

Dextropropoxyphene, a synthetic opioid analgesic, was commonly used for mild to moderate pain relief. Its combination with acetaminophen or aspirin was popular in some countries. However, due to its narrow therapeutic index, potential for abuse, and severe adverse effects, it has been withdrawn in several countries, including the United States and European Union. This case study highlights a clinical scenario involving dextropropoxyphene toxicity.

Case Presentation

- **Age/Sex**: 32-year-old female • **Medical History**:
  - Depression
  - Recent relationship issues
- **Presentation**: Brought to the Emergency Department (ED) after a suspected overdose of dextropropoxyphene, ingested with alcohol.

Pharmacology and Mechanism of Action **Class**:

Opioid analgesic.

Mechanism of Action: Acts on the central nervous system by binding to opioid receptors (primarily mu receptors), which inhibits the perception of pain.

Metabolism: Metabolized in the liver to form norpropoxyphene, which has a longer half- life and contributes to toxicity.

Excretion: Excreted via the kidneys.

Therapeutic Uses

Relief of mild to moderate pain.

Occasionally used as an antitussive (cough suppressant). Toxicity and Adverse Effects

Central Nervous System: Drowsiness, dizziness, confusion, and respiratory depression (especially in overdose).

Cardiotoxicity: Norpropoxyphene is associated with arrhythmias, cardiac arrest, and QT interval prolongation.

Overdose Risk: Narrow therapeutic index, with overdose leading to fatal respiratory depression and cardiac arrhythmias.

Addiction Potential: Habit-forming when misused.

Regulatory Status

Banned in Many Countries: India, the United States, and Europe have withdrawn dextropropoxyphene from the market due to the risks outweighing the benefits.

Reason for Withdrawal: Fatal overdose cases and reports of cardiotoxicity.

Case Study Example

Clinical Scenario

A 45-year-old woman presented to the emergency department following the
ingestion of 30 tablets of a combination analgesic containing dextropropoxyphene and acetaminophen, taken as a suicide attempt.

Symptoms:

Drowsiness, confusion, and slurred speech.Hypotension and bradycardia. Respiratory depression (respiratory rate: 8 breaths/min).

Electrocardiogram (ECG): QT prolongation and ventricular arrhythmias. Elevated liver enzymes due to acetaminophen toxicity.

Investigations

Blood Gas Analysis: Respiratory acidosis.

Toxicology Screen: Confirmed high plasma levels of dextropropoxyphene and norpropoxyphene.

ECG: Marked QT interval prolongation.

Liver Function Tests: Elevated transaminases due to acetaminophen hepatotoxicity.

4. Regulatory Gaps and Challenges

4.1 Weak Post-Marketing Surveillance

India lacks a robust post-marketing surveillance system to track adverse drug reactions effectively. This gap allows harmful drugs to remain on the market long after their dangers become evident elsewhere.

4.2 Pharmaceutical Industry Influence

The Indian pharmaceutical industry plays a significant role in the economy, often influencing regulatory decisions. The affordability of certain drugs like Pioglitazone means they continue to be sold, despite safety concerns, due to economic factors and the lack of safer alternatives.

4.3 Limited Public and Professional Awareness

Many healthcare providers and patients in India may not be fully aware of the risks associated with these banned drugs. Medical professionals may continue prescribing these drugs due to outdated guidelines or lack of access to the latest international research.

5. Impact on Public Health

5.1 Patient Safety Concerns

Pharmacovigilance is useful in assuring the safety of medicines and protecting the consumers from their harmful effects. A number of single drugs as well as fixed dose combinations have been banned from manufacturing, marketing and distribution in India. An important issue about the availability of banned drugs over the counter in

India is that sufficient adverse drug reactions data about these drugs have not been reported. The most common categories of drugs withdrawn in the last decade were nonsteroidal antiinflammatory drugs (28%), antidiabetics (14.28%), antiobesity (14.28%), antihistamines (14.28%), gastroprokinetic drugs (7.14%), breast cancer and infertility drugs (7.14%), irritable bowel syndrome and constipation drugs (7.14%) and antibiotics (7.14%). Drug withdrawals from market were made mainly due to safety issues involving cardiovascular events (57.14%) and liver damage (14.28%). Majority of drugs have been banned since 3-5 years in other countries but are still available for sale in India. The present study compares the drug safety monitoring systems in the developed countries such as the USA and UK and provides implications for developing a system that can ensure the safety and efficacy of drugs in India. Absence of a gold standard for a drug safety surveillance system, variations in culture and clinical practice across countries makes it difficult for India to completely adopt another country's practices. There should be a multidisciplinary approach towards drug safety that should be implemented throughout the entire duration spanning from drug discovery to usage by consumers.(A Ahmad, Isha Patel, Sudeepa Sanyal, R Balkrishnan, GP

Mohanta *Indian journal of pharmaceutical sciences 76 (5), 379, 2014)*

Poor-quality medicines present a serious public health problem, particularly in emerging economies and developing countries, and may have a significant impact on the national clinical and economic burden. Attention has largely focused on the increasing availability of deliberately falsified drugs, but substandard medicines are also reaching patients because of poor
manufacturing and quality-control practices in the production of genuine drugs (either branded or generic). Substandard medicines are widespread and represent a threat to health because they can inadvertently lead to healthcare failures, such as antibiotic resistance and the spread of disease within a community, as well as death or additional illness in individuals. This article reviews the different aspects of substandard drug formulation that can occur (for example, pharmacological variability between drug batches or between generic and originator drugs, incorrect drug quantity and presence of impurities). The possible means of addressing substandard manufacturing practices are also discussed. A concerted effort is required on the part of governments, drug manufacturers, charities and healthcare providers to ensure that only drugs of acceptable quality reach the patient.(Atholl Johnston, David W Holt *British journal of clinical pharmacology 78 (2), 218-243, 2014)*

5.2 Increased Healthcare Burden

Regulatory enforcement of product safety standards given health concerns, whether it is in romaine lettuce, smartphones or cars, is emerging to be a challenge for global public health. This is particularly true for developing economies with fragile institutions. In this context, recent studies on Indian pharmaceutical markets provide evidence suggesting that the sector is a hub for substandard quality of medicines. Departing from these prior studies which use randomly collected samples, we reinvestigate this question using novel pan-India market sales data of banned medicines from 0.75 million pharmacists and chemists in India. We find that indeed such medicines get sold in India even after bans are imposed on them in the period 2007 to 2013. However, there is a general decline in demand post ban for our focal molecules suggesting broad adherence to bans. We also observe regional heterogeneity in prevalence of banned medicines sold between rich and poor regions of India with the former counterintuitively showing more sales. That said, while Ozawa et al. (2018) argue that prevalence of substandard medicines is around 13% in low and middle-income countries, we find an infringement ratio which is more muted in India at about 5%. Finally, a regression-based examination suggests that prior firm presence in therapeutic markets and popularity of molecules positively impact the likelihood of sale of banned medicines in India. Our results are robust to alternative explanations and are substantiated with a theoretical set up examining firm trade-offs in the decision to infringe. India has recently been under the lens of the global access to medicines debate and our findings have important policy implications for global health.(Chirantan

Chatterjee, Debi Prasad Mohapatra, Manuel Estay *Social Science & Medicine 237, 112480, 2019)*

Over five decades of independence, India has made rapid strides in various sectors. However, its performance in social sectors and particularly the healthcare sector has not been too rosy. Being the State's responsibility the healthcare has traditionally been influenced by individual State's budgetary allocation. Consequently inter-state

disparity in availability and utilization of health services and health manpower are distinctly marked. This has implications for achievement of Health for All for the nation as a whole. Keeping in view the significance of studying inter-state variations in healthcare, this study focuses on the performance of healthcare sector in 15 major States in India. This is attempted through a comparative analysis of various parameters depicting availability of health services, their utilization and health outcomes. Our analysis depicts the prevalence of considerable inequity favoring high income group of States. In terms of healthcare resources, for instance, it indicates that the high income States hold a superior position in terms of: per capita government expenditure on medical and public health, total number of hospitals and dispensaries, per capita availability of beds in hospitals and dispensaries and health manpower in rural and urban areas. These parameters of availability have an impact on utilization levels and health outcomes in these States. A comparative profile of high and low income States as well as middle and low income States, both in rural and urban areas, reaffirms a greater financial burden in availing treatment at OPD and inpatient in low income States. In line with the higher financial burden and low per capita

health expenditure, the health outcome indicators also depict a disconcerting situation in regard to low income States. These States are marked by lower life expectancy and higher incidence of diseases as well as high mortality rates. In this regard, demand as well as supply side constraints are observed which restrain the optimum utilization of existing health services. Among the low income States the main constraints on the demand side include illiteracy, malnutrition, and lack of infrastructure in accessing the facilities. Certain state specific supply side factors add significantly to under-utilization in low income States. In some of the States, however, corrective actions have been initiated to overcome the problem of the quality and low utilization of health facilities. In due course of time, it is likely that proper implementation of these measures may result in improved utilization level of existing health services, which may be useful to improve health status indicators. Nonetheless, overcoming the current levels of regional disparities in healthcare across three income groups of States may also require additional resources. The latter could be mobilized through assistance of donor agencies and appropriate mix of social and private insurance. Ultimately mitigating the problem of regional disparities in healthcare and protecting the poor and vulnerable from financial burden may require establishing and maintaining proper linkages between socio-economic development and healthcare planning.(Brijesh C Purohit *Journal of Health & Social Policy 18 (3), 37-60, 2004)*

5.3 Ethical Considerations

The ethical implications of allowing banned drugs to circulate in the healthcare system are severe. Patients often do not receive adequate information about the risks, leading to uninformed consent and increased vulnerability.

We examine the ethical, social, and regulatory barriers that may hinder research on therapeutic potential of certain controversial controlled substances like marijuana, heroin, or ketamine. Hazards for individuals and society and potential adverse effects on communities may be good reasons for limiting access and justify careful monitoring of these substances. Overly strict regulations, fear of legal consequences, stigma associated with abuse and populations using illicit drugs, and lack of funding may, however, limit research on their considerable therapeutic potential. We review the surprisingly sparse literature and address the particular ethical concerns pertinent to research with illicit and addictive substances, such as undue inducement, informed consent, therapeutic misconception, and risk to participants, researchers, and institutions. We consider the perspectives of key research stakeholders and explore whether they may be infected with bias. We conclude by proposing an empirical research agenda to provide an evidentiary basis for ethical

reasoning.(Debbie Indyk, Henry Sacks, Rosamond *The American Journal of Bioethics 16 (4), 36-47, 2016)*

As the classification of mental disorders advances towards a disease model as promoted by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC), there is hope that a more thorough neurobiological understanding of mental illness may allow clinicians and researchers to determine treatment efficacy with less diagnostic variability. This paradigm shift has presented a variety of ethical issues to be considered in the

development of psychiatric drugs. These challenges are not limited to informed consent practices, industry funding, and placebo use. The consideration for alternative research models and quality of research design also present ethical challenges in the development of psychiatric drugs. The imperatives to create valid and sound research that justify the human time, cost, risk and use of limited resources must also be considered. Clinical innovation, and consideration for special populations are also important aspects to take into account. Based on the breadth of these ethical concerns, it is particularly important that scientific questions regarding the development of psychiatric drugs be answered collaboratively by a variety of stakeholders. As the field expands, new ethical considerations will be raised with increased focus on genetic markers, personalized medicine, patient-centered outcomes research, and tension over funding. We suggest that innovation in trial design is necessary to better reflect practices in clinical settings and that there must be an emphasized focus on expanding the transparency of consent processes, regard for suicidality, and care in working with special populations to support the goal of developing sound psychiatric drug therapies.(Felix Carrier, David Banayan, Randy Boley, Niranjan Karnik *Progress in neurobiology 152, 58-69, 2017)*

6. Proposed Solutions and Policy Recommendations

6.1 Strengthening Regulatory Frameworks

India's drug regulatory system needs to be aligned with global best practices. The CDSCO should adopt faster and more rigorous bans on harmful drugs, supported by real-time safety data and international research.

6.2 Enhancing Pharmacovigilance

A national-level pharmacovigilance system that actively monitors adverse drug reactions and rapidly responds to new data on drug safety is essential. This system should also involve healthcare professionals and public reporting.

The Aim of present work is to report Nimesulide a Nonsteroildal Anti Inflammatory Drug is being sold as over the counter drug has to banned completely due to occurrence of Nimesulide induced acute hepatitis. On February 12, 2011, the Union Ministry of Health and Family Welfare finally had decided to suspend the pediatric use of the Nimesulide suspension. From 10 March 2011 Nimesulide formulations are not indicated for human use in children below 12 years of age. On September 13, 2011 Madras High Court revoked a suspension on manufacture and sale of pediatric drugs Nimesulide and phenylpropanolamine (PPA). Though the government of India has banned the pediatric use of Nimesulide for common fever and pain due to its adverse effects on the liver, its usage by adults is being increased everyday without any prescription. The drug was banned in 2000 in various countries like Switzerland, Spain, United states etc, whereas in India it was banned in 2011 which was too late to be banned and still available in India for adult use despite of its hepatotoxicity and possible drug interactions.*(C Muralikrishna Goud, Syeda Mariya Ghazanfar)*

A Number of drug that are banned in abroad are freely available in the Indian market. The most pitiable feature is that use of these drugs are regularly causing long term implication for our physical health. Some of the common ones that are easily available and people use frequently without doctor's prescription are D-cold, Nimesulide and Analgin. These are use as pain killer but latest research shows that long term use of such medicines can affect human health in various ways by damaging liver, causing irregular heartbeats, depression, blood pressure fluctuations etc. This is the prime reason that most of European countries have disqualified and banned the manufacturing and consumption of these drugs. It has been recently pointed out that Indian drug regulatory authorities have refused to ban sale of 11 drug, including Furazolidone, Phenypropanolamine, Cisapride and Nimuselide, apart from over 80 drug combinations that are prohibited in other countries IPA have made various regulation and guideline for the control of these drug, but still they are in use because of lack of awareness in people.(Priya Diwedi *Critical review in pharmaceutical sciences 1 (3), 1-2, 2012)*

6.3 Public Education and Awareness

Awareness campaigns aimed at both healthcare professionals and the public can reduce the usage of banned drugs. These initiatives should inform people about safer alternatives and the potential risks associated with certain medications.

6.4 Introducing Safer Alternatives

To reduce the reliance on banned drugs, India must invest in research and development of safer and more effective alternatives. The government could provide subsidies or incentives to make these alternatives more accessible, especially in rural areas.

7. Conclusion

The persistence of banned drugs in India's healthcare system poses a significant risk to public health and highlights critical regulatory gaps. To protect patients and ensure the integrity of the healthcare system, immediate reforms are necessary. Strengthening the regulatory framework, enhancing pharmacovigilance, and raising awareness are vital

steps toward eliminating the dangers associated with these drugs. The responsibility lies not only with regulatory authorities but also with healthcare professionals, patients, and policymakers to push for a safer, more transparent pharmaceutical environment.

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