International Journal of Pharmacology and Clinical Research

ISSN Print: 2664-7613
ISSN Online: 2664-7621
Impact Factor: RJIF 8.29
IJPCR 2025; 7(2): 563-570
www.pharmacologyjournal.in
Received: 12-10-2025
Accepted: 15-11-2025

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A comprehensive review on withdrawn NSAIDs with emphasis on pharmacovigillance, safety signals and regulatory outcomes

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DOI: https://www.doi.org/10.33545/26647613.2025.v7.i2g.153

Abstract
Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most extensively prescribed therapeutic agents used for the management of inflammation, pain, and fever. Despite their wide utility, numerous NSAIDs have been withdrawn from the market due to serious and sometimes fatal adverse reactions. The mechanisms of these toxicities often involve the inhibition of protective prostaglandins, hepatic enzyme interference, and metabolic idiosyncrasies that remain undetected during preclinical testing.
This review provides a detailed pharmacological and toxicological evaluation of five banned NSAIDs *Nimesulide, Rofecoxib, Benoxaprofen, Phenylbutazone + Sodium Salicylate* and *Valdecoxib*. It focuses on their mechanism of action, surveillance data, and the subsequent regulatory decisions that led to their withdrawal. Information was compiled from scientific databases, clinical trial records, and official regulatory reports to ensure an evidence-based overview.
The review emphasizes how inadequate long-term safety monitoring and insufficient post-approval vigilance contributed to delayed recognition of severe toxicities such as hepatotoxicity, cardiovascular complications, and hematologic disorders. Furthermore, it discusses the global impact of these withdrawals on the evolution of modern pharmacovigilance systems, highlighting the transition from spontaneous adverse event reporting to structured global monitoring networks.
The findings underline the critical importance of continuous post-marketing evaluation, risk-benefit analysis, and judicious prescribing practices. Understanding these historical drug withdrawals not only safeguards patient health but also provides a valuable framework for future NSAID development and regulatory oversight.

Keywords: NSAIDs, Pharmacovigilance, banned drugs, adverse drug reactions, hepatotoxicity, cardiovascular risk, regulatory withdrawal

1. Introduction
Non-steroidal anti-inflammatory drugs (NSAIDs) represent an important therapeutic class used globally for management of pain, inflammation, and fever. Although pre-clinical and clinical trials provide extensive data on safety, these trials involve limited populations and controlled conditions, making rare but serious adverse events difficult to detect.
As NSAIDs became widely prescribed, several agents showed unexpected severe toxicity in the general population, resulting in global withdrawals. Drug withdrawal is rare yet crucial regulatory process triggered when the risk associated with a marketed drug outweighs its therapeutic benefit. This highlights the importance of post-marketing surveillance (Phase IV) and pharmacovigilance systems in identifying late-emerging drug safety issues.
This review analyzes five globally withdrawn NSAIDs, focusing on their pharmacological properties, safety concerns, and regulatory outcomes, thereby strengthening understanding of drug safety evaluation.

This review focuses on five important NSAIDs withdrawn globally after substantial post-marketing safety signals:
- Nimesulide
- Rofecoxib
- Benoxaprofen
- Phenylbutazone with Sodium Salicylate.

- Valdecoxib

Each drug is evaluated for:-

- History & development
- Pharmacodynamics
- Pharmacokinetics
- Adverse drug reactions
- Reasons for withdrawal
- Post-marketing surveillance findings
- Final regulatory outcome

This scientific assessment reinforces the importance of rigorous pharmacovigilance systems and structured ADR reporting to safeguard public health.

2. Nimesulide

2.1 Introduction and Historical Background

Nimesulide, a sulfonanilide derivative and selective COX-2 inhibitor, was first introduced in Italy in 1985 as an anti-inflammatory, analgesic, and antipyretic agent. Its introduction was based on the hypothesis that selective inhibition of COX-2 would minimize the gastrointestinal adverse effects commonly seen with non-selective NSAIDs. The drug gained rapid global acceptance and was marketed in over 50 countries, including India, for the treatment of osteoarthritis, musculoskeletal pain, and dysmenorrhea. However, post-marketing surveillance soon identified serious hepatic adverse effects, leading to increasing safety concerns. By the early 2000s, several European countries, including Finland and Spain, began restricting or suspending its use due to reports of fatal hepatotoxicity.

2.2 Chemical and Pharmacological Profile

Chemically, Nimesulide is N-(4-nitro-2-phenoxyphenyl) methanesulfonamide ($C_{13}H_{12}N_2O_5S$) with a molecular weight of 308.31 g/mol. It exhibits a moderate degree of COX-2 selectivity and possesses additional pharmacodynamic actions such as inhibition of myeloperoxidase activity, reduction of tumor necrosis factor-alpha (TNF-α), and scavenging of free radicals attributes that contribute to its anti-inflammatory efficacy.

Pharmacokinetics

- **Absorption:** Rapidly and completely absorbed following oral administration; peak plasma concentration achieved within 2-3 hours.
- **Distribution:** Approximately 97.5% plasma-protein bound, indicating extensive tissue distribution.
- **Metabolism:** Undergoes hepatic biotransformation primarily via CYP2C9 to form 4-hydroxy-nimesulide, an active metabolite responsible for most of its pharmacological activity.
- **Elimination:** Excreted through urine and bile; elimination half-life ranges between 2-5 hours.
- Nimesulide's metabolic dependence on hepatic enzymes makes it particularly susceptible to accumulation and toxicity in patients with hepatic dysfunction.

2.3 Therapeutic Applications

Initially approved for short-term management of acute pain, osteoarthritis, and primary dysmenorrhea, Nimesulide demonstrated efficacy comparable to diclofenac and ibuprofen. It was also marketed as a pediatric formulation (suspension) for fever management in India. However, long-term or high-dose therapy showed no additional clinical benefit, while markedly increasing the risk of hepatic damage.

2.4 Adverse Drug Reactions (ADR)

The most significant toxicity associated with Nimesulide is hepatotoxicity, characterized by elevated liver transaminases, cholestatic jaundice, and in severe cases, fulminant hepatic failure. Clinical presentation includes fatigue, anorexia, nausea, vomiting, and jaundice. Histopathological findings revealed centrilobular necrosis and bile duct proliferation.

Other observed ADRs include:

- Gastrointestinal bleeding and gastritis (less frequent than non-selective NSAIDs)
- Hypersensitivity reactions such as rash, pruritus, and urticaria
- Renal impairment, particularly in dehydrated or comorbid patients
- In a post-marketing review, hepatic adverse reactions accounted for over 40% of serious ADR reports related to Nimesulide.

2.5 Post-marketing surveillance and regulatory assessment

Between 1999 and 2011, multiple European regulatory authorities, including the European Medicines Evaluation Agency (EMEA), analyzed reports from pharmacovigilance databases. The WHO Uppsala Monitoring Centre (UMC) confirmed more than 700 cases of hepatic injury and over 60 deaths linked to Nimesulide use.

In India, the CDSCO (Central Drugs Standard Control Organization) initiated a nationwide review in 2011 following pediatric fatalities and suspended all pediatric formulations. The adult formulations were allowed to continue for short-term use only (≤ 15 days) under strict prescription guidelines.

The European Medicines Agency (EMA) re-evaluated its safety in 2011, concluding that hepatotoxicity risk outweighed potential benefits, resulting in suspension in several EU countries.

2.6 Mechanism of Hepatotoxicity

Nimesulide undergoes bioactivation to reactive nitroaromatic intermediates which bind covalently to hepatic proteins, generating oxidative stress and mitochondrial dysfunction. This results in hepatocellular necrosis and immune-mediated injury. The process is idiosyncratic, unrelated to dose, and unpredictable, which complicates early detection during pre-marketing studies.

2.7 Reason for Ban

The decision to restrict or ban Nimesulide was primarily based on unacceptable risk-benefit ratio. Despite comparable efficacy to other NSAIDs, it carried a disproportionate incidence of severe hepatic events, including death. Its pediatric use was considered especially unsafe due to immature metabolic pathways in children. Consequently, Nimesulide was banned in Finland (2002), Spain (2003), and India (For pediatric use, 2011), and later suspended in several European markets.

2.8 Final Outcome and Current Status

Nimesulide remains available in a few countries for short-term treatment of pain and inflammation, with mandatory hepatic monitoring. It is prohibited for chronic use or pediatric administration. The Nimesulide case remains a landmark in NSAID pharmacovigilance, emphasizing that preclinical safety does not always predict post-marketing outcomes. Its withdrawal reshaped global regulatory frameworks and highlighted the crucial need for continuous adverse event monitoring to ensure patient safety.

3. Roficoxib

3.1 Introduction and Historical Background

Rofecoxib, commercially known as Vioxx, was a selective cyclooxygenase-2 (COX-2) inhibitor developed by Merck & Co. and approved by the U.S. FDA in May 1999. It was introduced with the aim of providing potent anti-inflammatory and analgesic activity similar to traditional NSAIDs but with reduced gastrointestinal toxicity. Rofecoxib quickly became one of the top-selling pain medications worldwide, particularly for arthritis, acute pain, and dysmenorrhea.

However, within a few years of marketing, evidence emerged linking Rofecoxib to a significant increase in cardiovascular events, including myocardial infarction and stroke. Following multiple clinical trial findings and post-marketing reports, the drug was voluntarily withdrawn from the market on September 30, 2004, in one of the most notable drug withdrawals in pharmaceutical history.

3.2 Chemical and Pharmacological Profile

Chemically, Rofecoxib is 4-(4'-methylsulfonylphenyl)-3-phenyl-2(5H)-furanone ($C_{17}H_{14}O_4S$) with a molecular weight of 314.36 g/mol. It selectively inhibits the COX-2 isoenzyme, thereby preventing prostaglandin synthesis responsible for pain and inflammation, while sparing COX-1 responsible for gastric protection and platelet aggregation.

Pharmacokinetics

- **Absorption:** Rapidly absorbed after oral administration with peak plasma concentrations at 2-3 hours.
- **Bioavailability:** ~93%.
- **Distribution:** Highly protein-bound (~87% to albumin).
- **Metabolism:** Extensively metabolized in the liver via CYP3A4 and non-CYP dependent oxidation.
- **Elimination:** Excreted mainly in urine; elimination half-life of 17 hours allows once-daily dosing.

3.3 Therapeutic Applications

Rofecoxib was approved for the management of osteoarthritis, acute pain, rheumatoid arthritis, and dysmenorrhea. Due to its long half-life, once-daily dosing improved patient compliance, and it showed lower incidence of gastric ulceration compared to ibuprofen or naproxen. However, this clinical advantage was overshadowed by emerging cardiovascular risks during chronic therapy.

3.4 Adverse Drug Reactions (ADR)

The primary safety concern with Rofecoxib involved cardiovascular toxicity, though other adverse effects were also documented.

Major ADRs include

- **Cardiovascular:** Myocardial infarction, thromboembolic stroke, hypertension, congestive heart failure.
- **Gastrointestinal:** Dyspepsia, abdominal pain (less frequent than traditional NSAIDs).
- **Renal:** Fluid retention, edema, and worsening renal function in predisposed patients.
- **Dermatologic:** Rash and pruritus in some users.

The VIGOR (Vioxx Gastrointestinal Outcomes Research) trial, published in The New England Journal of Medicine (2000) [9], first reported a fivefold increase in myocardial infarction risk in Rofecoxib users compared with naproxen.

3.5 Post-Marketing Surveillance and Regulatory Assessment

After its approval, numerous studies and spontaneous reports confirmed cardiovascular risk.

- The APPROVe (Adenomatous Polyp Prevention on Vioxx) trial in 2004 revealed a doubling of cardiovascular event incidence in long-term users.
- The FDA Adverse Event Reporting System (AERS) database accumulated over 27,000 cardiovascular reports linked to Rofecoxib.
- Independent researchers estimated that 88,000-139,000 heart attacks could have been related to its use in the U.S. alone.

In response, the FDA conducted extensive reviews, and Merck voluntarily withdrew Rofecoxib from the global market in September 2004.

3.6 Mechanism of Cardiovascular Toxicity

Rofecoxib's selective inhibition of COX-2 suppresses prostacyclin (PGI_2) synthesis in vascular endothelium, which normally inhibits platelet aggregation and promotes vasodilation. However, thromboxane A_2 synthesis (mediated by COX-1) remains unopposed, resulting in a prothrombotic state.

This imbalance between PGI_2 and TXA_2 leads to vasoconstriction, platelet aggregation, and increased risk of thrombosis and myocardial infarction.

3.7 Reason for ban

The decision to withdraw Rofecoxib was based on overwhelming evidence of cardiovascular harm without significant improvement in overall therapeutic benefit. Despite effective pain relief, its use posed unacceptable risks in patients with or without preexisting heart disease. Regulatory authorities concluded that the risk-benefit ratio was unfavorable, and safer alternatives were available.

3.8 Final Outcome and Regulatory Impact

The Rofecoxib withdrawal remains a turning point in modern pharmacovigilance. It prompted regulatory agencies like the FDA, EMA, and CDSCO to strengthen post-marketing safety monitoring and to require cardiovascular outcome studies for all COX-2 inhibitors.

Merck faced thousands of legal claims and significant financial losses. Subsequent investigations criticized inadequate data disclosure during early trials. The case emphasized the ethical obligation of transparency and patient safety in drug development.

Today, Rofecoxib is completely withdrawn from all markets worldwide, serving as a permanent example of how selective pharmacological targeting does not guarantee safety.

4. Benoxaprofen

4.1 Introduction and Historical Background

Benoxaprofen, a propionic acid derivative NSAID, was first synthesized by Eli Lilly & Co. in the early 1970s and marketed under the brand names Oraflex (U.S.) and Opren (U.K.) in 1980. It was primarily indicated for the treatment of osteoarthritis, rheumatoid arthritis, and musculoskeletal pain. Initially hailed for its long half-life and potent anti-inflammatory activity, Benoxaprofen became popular for once-daily dosing. However, soon after approval, numerous reports of hepatotoxicity, photosensitivity, and fatal jaundice began to surface, particularly among elderly patients. The situation escalated rapidly, and by 1982, the drug was withdrawn worldwide after hundreds of serious and fatal hepatic cases were reported.

4.2 Chemical and Pharmacological Profile

Chemically, Benoxaprofen is 2-[4-(2-chlorophenyl) phenoxy] propionic acid ($C_{16}H_{12}ClO_3$), belonging to the arylpropionic acid NSAID class. It acts as a non-selective inhibitor of both COX-1 and COX-2 enzymes, thereby suppressing prostaglandin synthesis responsible for inflammation, pain, and fever.

Pharmacokinetics

- **Absorption:** Slowly but almost completely absorbed after oral administration.
- **Distribution:** Highly protein-bound (~99%).
- **Metabolism:** Minimal hepatic metabolism; predominantly excreted unchanged.
- **Elimination:** Very slow elimination via urine and bile; half-life ranges from 30 to 35 hours, leading to significant accumulation on repeated dosing.

This unusually long half-life and accumulation tendency were later identified as major contributors to its toxicity.

4.3 Therapeutic Uses

Benoxaprofen was prescribed for osteoarthritis, rheumatoid arthritis, and musculoskeletal disorders. Its once-daily dosing and rapid symptom relief led to widespread early use, especially among geriatric patients who were more vulnerable to hepatic and renal side effects.

4.4 Adverse Drug Reactions (ADR)

The most serious and well-documented adverse reaction of Benoxaprofen is hepatotoxicity, often presenting as cholestatic jaundice, hepatic necrosis, and hepatic failure.

Other significant ADRs include:-

- **Dermatologic:** Photosensitivity reactions, severe rash, and exfoliative dermatitis.
- **Renal:** Interstitial nephritis and renal failure.
- **Hematologic:** Leukopenia and eosinophilia in isolated cases.

The British Medical Journal (BMJ) in 1982 published multiple case reports of fatal hepatic injury in elderly patients taking Benoxaprofen. Liver biopsies revealed cholestasis and hepatocellular necrosis.

4.5 Post-Marketing Surveillance and Regulatory Review

Post-marketing data collected in 1981-1982 revealed an alarming number of hepatic and skin toxicity cases.

- In the UK, the Committee on Safety of Medicines (CSM) received 350 serious hepatic injury reports and 18 confirmed deaths within two years of launch.
- In the U.S., the FDA received 31 death reports within 11 months, many linked to hepatic failure and photosensitivity.
- A Lancet editorial in 1982 criticized inadequate pre-approval studies and poor post-market safety monitoring.

Following these findings, both FDA and UK CSM conducted urgent reviews, leading Eli Lilly to voluntarily withdraw Benoxaprofen in August 1982.

4.6 Mechanism of toxicity

Benoxaprofen is metabolized through oxidative pathways, generating reactive acyl glucuronides that covalently bind to hepatic proteins. These reactive metabolites cause oxidative stress, mitochondrial damage, and lipid peroxidation in hepatocytes. Additionally, the drug exhibits phototoxic properties due to its benzoxazole structure, which upon UV exposure leads to free radical formation and skin damage. Elderly patients, having slower metabolic clearance, were particularly susceptible to accumulation and toxicity.

4.7 Reason for Ban

The decision to ban Benoxaprofen was based on:-

- High incidence of fatal hepatic failure and photosensitivity reactions.
- Prolonged half-life leading to accumulation and unpredictable toxicity.
- Lack of reliable monitoring or early detection of hepatic injury.

Given the availability of safer NSAIDs, the risk-benefit ratio was clearly unfavorable. Consequently, the drug was withdrawn globally in 1982.

4.8 Final Outcome and Regulatory Impact

The Benoxaprofen case marked one of the earliest large-scale post-marketing drug withdrawals in modern history. It led to major changes in pharmacovigilance policies worldwide, including:-

- Mandatory spontaneous reporting systems for ADRs (e.g., Yellow Card Scheme in the UK).
- Stricter post-approval safety monitoring requirements by FDA and CSM.
- Recognition of the importance of geriatric pharmacokinetics in drug safety assessment.

The Benoxaprofen tragedy became a benchmark for understanding how metabolic accumulation and delayed toxicity can evade detection in clinical trials. It profoundly shaped regulatory vigilance for future NSAID development.

5. Phenylbutazone and Sodium Salicylate Combination

5.1 Introduction and Historical Background

The combination of Phenylbutazone and Sodium Salicylate was among the earliest anti-inflammatory formulations

developed for the management of rheumatoid arthritis, ankylosing spondylitis, and acute gout. Both drugs belong to the non-steroidal anti-inflammatory drug (NSAID) class but differ in structure and mechanism.

Phenylbutazone, introduced in the 1950s, was one of the first potent pyrazolidinedione derivatives, while Sodium Salicylate, a salicylic acid salt, was one of the oldest anti-inflammatory agents derived from natural salicylates. The combination aimed to achieve enhanced efficacy with balanced toxicity; however, it soon became evident that the additive adverse effects outweighed therapeutic benefits.

By the 1970s, this combination was associated with severe hematological and gastrointestinal complications, leading to restrictions and eventual withdrawal from many markets.

5.2 Chemical and Pharmacological Profile

Phenylbutazone ($C_{19}H_{20}N_2O_2$) acts by non-selectively inhibiting cyclooxygenase (COX-1 and COX-2), suppressing prostaglandin synthesis and providing strong anti-inflammatory and analgesic effects.

Sodium Salicylate ($C_7H_5NaO_3$), a derivative of salicylic acid, acts similarly by inhibiting COX enzymes and interfering with NF-κB activation, contributing to anti-inflammatory and antipyretic effects.

Pharmacokinetics of the Combination:-

- **Absorption:** Both drugs are rapidly absorbed orally.
- **Distribution:** Highly protein-bound (> 95%), allowing tissue penetration.
- **Metabolism:** Phenylbutazone undergoes hepatic metabolism to oxyphenbutazone; Sodium Salicylate is converted to salicylic acid.
- **Elimination:** Primarily renal; prolonged half-life of phenylbutazone (~70 hours) leads to cumulative toxicity during chronic use.

The combination was expected to produce synergistic efficacy but instead showed increased risk of systemic toxicity, especially in elderly and debilitated patients.

5.3 Therapeutic Uses

This combination was indicated for the treatment of chronic inflammatory conditions such as rheumatoid arthritis, ankylosing spondylitis, and acute musculoskeletal disorders. In some cases, it was used for gout and postoperative inflammation. However, because of serious side effects, it was soon replaced by safer NSAIDs like ibuprofen and indomethacin.

5.4 Adverse Drug Reactions (ADR)

Adverse effects from the combination primarily involved hematologic, gastrointestinal, renal, and hypersensitivity reactions.

Major Reported ADRs

- **Hematologic toxicity:** Aplastic anemia, agranulocytosis, leukopenia, thrombocytopenia.
- **Gastrointestinal:** Peptic ulceration, GI bleeding, nausea, vomiting.
- **Renal:** Acute kidney injury, sodium retention, and edema.
- **Dermatologic:** Rash, Urticaria and Stevens-Johnson syndrome (rare).

Phenylbutazone's bone marrow suppression potential, combined with salicylate-induced gastric mucosal irritation, created a high-risk toxicity profile that was unacceptable for long-term therapy.

5.5 Post-Marketing Surveillance and Safety Findings

During post-marketing surveillance in the 1960s and 1970s, numerous cases of fatal aplastic anemia and GI hemorrhage were reported.

- The WHO pharmacovigilance database and U.S. FDA reports linked the combination to > 200 confirmed cases of life-threatening blood dyscrasias.
- Several European countries, including the UK, recorded mortality rates of up to 10% in patients developing aplastic anemia from Phenylbutazone use.

Consequently, the FDA restricted Phenylbutazone use in 1973 to hospitalized patients only and later banned all fixed-dose combinations containing Phenylbutazone and Sodium Salicylate.

5.6 Mechanism of Toxicity

The mechanism involves idiosyncratic bone marrow suppression due to immune-mediated destruction of hematopoietic stem cells. Phenylbutazone forms reactive metabolites that bind to marrow proteins, triggering an autoimmune response.

Additionally, salicylates potentiate gastric acid secretion and inhibit platelet aggregation, increasing bleeding risk.

The dual toxicity profile led to cumulative hematologic and gastrointestinal injury even at therapeutic doses.

5.7 Reason for Ban

The combination was banned because of:-

- High incidence of fatal aplastic anemia and agranulocytosis.
- Increased risk of gastrointestinal bleeding due to additive mucosal injury.
- Lack of any significant efficacy advantage over single-drug therapy.
- Safer NSAIDs becoming available with better safety margins.

By the late 1970s, most regulatory authorities, including the FDA, EMA, and CDSCO, permanently withdrew the combination.

5.8 Final Outcome and Regulatory Impact

The withdrawal of Phenylbutazone-Sodium Salicylate combination marked an important regulatory milestone. It emphasized the dangers of combining two potent NSAIDs with overlapping toxicity profiles.

Following its ban, global agencies implemented stricter combination drug approval guidelines, requiring:-

- Justification of synergistic efficacy.
- Independent toxicity evaluation of each component.
- Mandatory post-marketing pharmacovigilance reports.

The case also strengthened hematologic monitoring protocols and advanced early-warning systems for rare but severe adverse drug reactions.

6. VALDECOXIB (BEXTRA)

6.1 Introduction and Historical Background

Valdecoxib, marketed under the brand name Bextra, is a selective cyclooxygenase-2 (COX-2) inhibitor developed by Pfizer Inc. It was approved by the U.S. FDA in November 2001 for the treatment of osteoarthritis, rheumatoid arthritis, and primary dysmenorrhea.

The drug was part of the "coxib" generation, designed to offer anti-inflammatory and analgesic efficacy comparable to traditional NSAIDs, but with reduced gastrointestinal toxicity. Despite its promising start, post-marketing studies soon revealed serious and sometimes fatal cardiovascular and dermatologic adverse events, including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).

Following increasing reports of life-threatening hypersensitivity reactions and thrombotic risks, the FDA requested market withdrawal in April 2005, and Pfizer voluntarily discontinued Valdecoxib worldwide.

6.2 Chemical and Pharmacological Profile

Chemically, Valdecoxib is 4-(5-methyl-3-phenylisoxazol-4-yl) benzenesulfonamide ($C_{16}H_{14}N_2O_4S$), a potent and selective COX-2 inhibitor.

Mechanism of Action

By selectively inhibiting COX-2, Valdecoxib reduces the synthesis of inflammatory prostaglandins, providing effective anti-inflammatory and analgesic effects while sparing COX-1 activity that protects the gastric mucosa.

Pharmacokinetics

- **Absorption:** Rapidly absorbed after oral administration; bioavailability ~83%.
- **Distribution:** Highly protein-bound (~98%).
- **Metabolism:** Extensively metabolized in the liver via CYP3A4 and CYP2C9, forming active metabolites such as parecoxib.
- **Elimination:** Excreted through renal and fecal routes; elimination half-life ~8-11 hour.

6.3 Therapeutic Uses

Valdecoxib was used to manage arthritis-related pain, postoperative pain, and dysmenorrhea. Its injectable prodrug, parecoxib, was approved for short-term pain control in hospitalized patients.

Although effective for inflammation and pain, reports soon indicated serious skin and cardiovascular side effects, even at therapeutic doses.

6.4 Adverse Drug Reactions (ADR)

Valdecoxib was associated with several serious adverse effects:-

- **Dermatologic:** Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), exfoliative dermatitis.
- **Cardiovascular:** Myocardial infarction, stroke, thrombosis, and edema.
- **Hepatic:** Elevated liver enzymes.
- **Gastrointestinal:** Dyspepsia and abdominal discomfort.

The FDA MedWatch database recorded over 120 severe skin reaction cases and multiple cardiovascular deaths within the first few years of marketing.

6.5 Post-Marketing Surveillance and Regulatory Review

Post-marketing surveillance played a crucial role in identifying Valdecoxib's safety concerns:

- FDA and EMA received extensive reports of SJS/TEN, including several fatalities.
- A cardiovascular safety evaluation following parecoxib/valdecoxib use in post-surgical patients revealed a significant increase in myocardial infarction incidence.

Following the withdrawal of Rofecoxib in 2004, regulatory agencies intensified scrutiny of all COX-2 inhibitors, resulting in suspension of Valdecoxib in April 2005.

In India, CDSCO issued safety advisories against its use, aligning with international regulatory decisions.

6.6 Mechanism of Toxicity

The drug's dual toxicity profile stems from both immunologic hypersensitivity and vascular imbalance:

- Skin reactions (SJS/TEN) are mediated through reactive metabolites that trigger immune-mediated keratinocyte apoptosis.
- Cardiovascular events occur due to suppression of endothelial prostacyclin (PGI_2) synthesis, leading to vasoconstriction and thrombosis.

These effects were amplified in predisposed patients, such as those with cardiac comorbidities or prior allergic conditions.

6.7 Reason for Ban

Valdecoxib was banned due to:-

- Fatal cases of Stevens-Johnson syndrome and toxic epidermal necrolysis.
- Increased incidence of myocardial infarction and stroke.
- Lack of any substantial benefit over safer COX-2 inhibitors.
- Inadequate risk mitigation despite labeling warnings.

Following global evaluation, FDA and EMA determined that the risk-benefit ratio was unacceptable, resulting in complete market withdrawal.

6.8 Final Outcome and Regulatory Impact

The Valdecoxib case reinforced the urgent need for long-term cardiovascular and hypersensitivity assessment of COX-2 inhibitors.

Post-withdrawal reforms included:-

- Requirement of dedicated cardiovascular safety trials for all COX-2 drugs.
- Strengthened pharmacovigilance reporting obligations.
- Greater transparency in publishing adverse event data by pharmaceutical companies.

Valdecoxib's withdrawal, following that of Rofecoxib, permanently changed regulatory perspectives on selective COX-2 inhibitors, underscoring the delicate balance between efficacy and safety.

7. Table

Table 1: Summary of withdrawn NSAIDS and key reasons

Drug	Year of Withdrawal	Raeson for Ban	Major ADRs
Nimesulide	2011-2013	Hepatotoxicity	Liver Failure
Rofecoxib	2004	Cardiovascular toxicity	MI, Stroke
Benoxaprofen	1982	Hepatotoxicity & Phototoxicity	Fatal liver injury
Phenylbutazone +Sodium salicylate	1983-85	Hematotoxicity	Agranulocytes
Valdecoxib	2005	SJS/TEN +CV risk	Severe Skin Reactions

Table 2: Post marketing safety signals

Drug	Safety Signal Source	Major Finding
Nimesulide	WHO-vigibase	Severe hepatic injury
Roficoxib	VIGOR &APPROVe	Increased CV events
Benoxaprofen	UK yellow card	Elderly Liver Failure
Phenylbutazone combo.	Medwatch	Agranulocytes
Valdecoxib	FDA reports	SJS/TEN &CV risk

8. Discussion

The review of five withdrawn non-steroidal anti-inflammatory drugs (NSAIDs) *Nimesulide*, *Rofecoxib*, *Benoxaprofen*, *Phenylbutazone* + *Sodium Salicylate* and Valdecoxib reveals that post-marketing pharmacovigilance plays a crucial role in ensuring long-term drug safety. Although all these drugs demonstrated strong preclinical and clinical efficacy profiles, their severe toxicities emerged only after widespread clinical use.

The pattern of toxicity observed among these agents highlights three critical aspects:-

- Hepatotoxicity (Nimesulide and Benoxaprofen) resulting from reactive metabolites and oxidative stress.
- Cardiovascular toxicity (Rofecoxib and Valdecoxib) due to selective COX-2 inhibition, causing prostacyclin suppression and thrombotic risk.
- Hematologic toxicity (Phenylbutazone + Sodium Salicylate) associated with bone marrow suppression and immune-mediated cytopenias.

These outcomes collectively demonstrate that selective enzyme inhibition and short-term trials cannot reliably predict rare or delayed toxicities. The inability to detect idiosyncratic reactions during pre-approval stages underscores the importance of robust post-marketing surveillance systems.

Furthermore, these drug withdrawals led to a paradigm shift in the global pharmacovigilance framework, strengthening safety protocols such as mandatory adverse event reporting, electronic data mining, and risk management plans (RMPs). They also promoted more stringent approval procedures for high-risk therapeutic classes, particularly NSAIDs.

The comparative analysis confirms that despite advances in molecular drug design, no pharmacological selectivity can fully eliminate systemic toxicity without continuous monitoring. The lessons learned from these cases continue to guide the development and regulation of safer anti-inflammatory agents.

9. Conclusion

The collective evidence from withdrawn NSAIDs emphasizes the delicate balance between therapeutic efficacy and patient safety. While all five agents *Nimesulide*, *Rofecoxib*, *Benoxaprofen*, *Phenylbutazone* + *Sodium Salicylate* and Valdecoxib provided effective pain relief, each exhibited serious, sometimes fatal adverse effects that outweighed their benefits.

The withdrawal of these drugs not only protected patients from further harm but also reshaped the global approach to drug safety evaluation. These cases highlight the need for long-term safety studies, early detection of adverse reactions, and continuous education of healthcare professionals about rational drug use.

In the modern era of pharmacovigilance, the ultimate goal is not only to develop effective drugs but also to ensure risk-benefit optimization throughout their lifecycle. Continuous post-marketing monitoring, transparent reporting, and collaborative regulatory vigilance remain essential pillars in preventing future drug-related tragedies.

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