EVALUATION AND REGULATORY STATUS OF THE BANNED COMBINATION OF PCM & ACECLOFENAC

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Abstract

The fixed-dose combination (FDC) of Paracetamol (PCM) and Aceclofenac has beewn widely used for pain and inflammatory conditions. However, scientific evaluation has raised concerns regarding its safety, pharmacological redundancy, and risk of adverse effects. Studies indicate that combining PCM with Aceclofenac offers no significant therapeutic advantage over individual drugs. Moreover, the combination increases the risk of hepatotoxicity and gastrointestinal complications. Regulatory bodies in India, including the Drugs Technical Advisory Board (DTAB), reviewed its risk–benefit profile. Based on evidence, the Government of India banned this FDC citing lack of rationality and heightened safety risks. The ban aligns with global regulatory standards emphasizing rational drug therapy. This evaluation highlights the importance of scientific scrutiny for FDCs to ensure public health safety

INTRODUCTION

Overview of PCM and Aceclofenac: The Paracetamol (PCM) + Aceclofenac combination is a widely used analgesic (pain reliever), anti-inflammatory, and antipyretic (fever reducer) medication. This combination provides enhanced pain relief by targeting chemical substances that causes both pain and inflammation in the body, making it more effective than paracetamol alone.

1.Paracetamol (Acetaminophen) Mechanism:

-Primarily acts on the central nervous system (CNS). -Inhibits the enzyme cyclooxygenase (COX) in the brain, reducing prostaglandin synthesis. -Prostaglandins are chemicals that transmit pain signals and regulate body temperature. -This results in pain relief (analgesic effect) and fever reduction (antipyretic effect).Has minimal anti-inflammatory action because it does not significantly inhibit COX peripheral tissues

2. Aceclofenac Mechanism:

A Non-Steroidal Anti-Inflammatory Drug (NSAID) that inhibits COX-2 enzymes. COX enzymes are responsible for prostaglandin production, which causes pain, inflammation, and fever. By reducing prostaglandin E2 level and IL-1Beta and TNF from Arachidonic Acid pathway, it provides strong anti-inflammatory and analgesic effects. It has minimal central action as compared to its peripheral action.

3. Synergistic Effect of the Combination

✓ Paracetamol acts centrally → Blocks pain signals in the brain and reduces fever.

✓ Aceclofenac acts peripherally → Reduces inflammation and pain at the site of injury

. ✓ Together, they provide stronger pain relief than when used alone, making them effective for conditions like menstrual cramps, headaches, muscle pain, mild migrain

Importance of Combination

✓ Stronger & Faster Pain Relief Paracetamol acts centrally (brain), while Aceclofenac works both centrally and peripherally (site of pain). This dual action provides better pain control than when taken individually

✓ Effective for Multiple Conditions Used in treating menstrual pain, headaches, dental pain, arthritis, muscle pain, post-operative pain, migrain and fever

✓ Fever Reduction & Inflammation Control Paracetamol reduces fever by acting on the hypothalamus (temperature control center in the brain) Aceclofenac controls inflammation, helping to reduce swelling and pain.

✓ Better Alternative to Stronger NSAIDs Compared to other NSAIDs like ibuprofen, this combination is relatively gentler on the stomach when taken with food. However, it should still be used cautiously in patients with gastric issues.

✓ Useful in Short-Term Pain Management Provides quick symptom relief, making it beneficial for acute pain conditions without needing stronger opioids.

➢ PARACETAMOL Chemical Structure

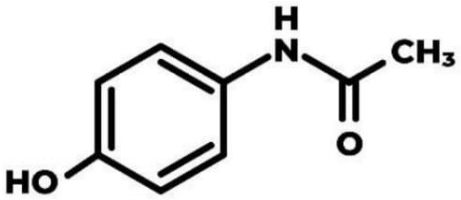
The chemical structure of Paracetamol (also known as Acetaminophen) is C8H9NO2. It features a benzene ring substituted with a hydroxyl group (-OH) and an amide group (-NHCOCH3). Here's a breakdown of the structure: •

Benzene ring: A six-carbon aromatic ring. • Hydroxyl group (-OH): Attached at one position on the ring. • Amide group (-NHCOCH3): Connected via a nitrogen atom.

Mechanism of action Paracetamol (also known as acetaminophen) primarily acts as an analgesic (pain reliever) and antipyretic (fever reducer). Unlike NSAIDs, it has minimal anti-inflammatory effect

1. Absorption & Metabolism After oral ingestion, PCM is rapidly absorbed from the gastrointestinal tract (small intestine). It undergoes hepatic metabolism (liver), primarily via: Glucuronidation & Sulfation (major pathways, producing inactive metabolites). Cytochrome P450 (CYP2E1) pathway (minor pathway, producing NAPQI, a toxic metabolite that is detoxified by glutathione).

2. Central Action (CNS) – COX Inhibition PCM weakly inhibits cyclooxygenase (COX) enzymes in peripheral tissues but exerts its main effects centrally (in the brain) by: Inhibiting COX-3 (a variant of COX-1 and COX-2 found in the CNS). Reducing prostaglandin (PGE2) synthesis in the hypothalamus, leading to its antipyretic



Paracetamol

3. Activation of Descending Pain Modulation Pathways Paracetamol gets converted to AM404 (active metabolite) in the brain, which: Activates TRPV1 receptors (linked to pain relief). Enhances endocannabinoid system activity, which helps in analgesia.

4. Fever Reduction (Antipyretic Effect) Fever is caused by increased PGE2 levels in the hypothalamus, which raises the body's temperature set point. PCM inhibits PGE2 synthesis, thereby resetting the hypothalamic temperature center to normal and reducing fever.
Summary of Effects
✓ Analgesic Effect → Inhibits COX enzymes in the CNS, reducing pain perception.
✓ Antipyretic Effect → Lowers PGE2 in the hypothalamus, reducing fever.
✓ Minimal Anti-inflammatory Action → Weak peripheral COX inhibition.

Pharmacokinetic and Pharmacodynamic effect Paracetamol (PCM), also known as acetaminophen, has well-characterized pharmacokinetics (PK) and pharmacodynamics (PD) properties. Pharmacokinetics (PK) of Paracetamol
1. Absorption Rapidly absorbed from the gastrointestinal (GI) tract, mainly in the small intestine. Peak plasma concentration occurs within 30 minutes to 2 hours after oral administration. Bioavailability is around 60-90%, depending on the formulation and individual metabolism.
2. Distribution Widely distributed in body fluids and tissues. Volume of distribution (Vd) is 0.9-1.0 L/kg. Poor plasma protein binding (~10-25%) at therapeutic doses but increases in overdose.
3. Metabolism Primarily metabolized in the liver via: Glucuronidation (45-55%) → forms inactive glucuronide conjugates. Sulfation (20-30%) → forms sulphate conjugates. Cytochrome P450 (CYP2E1) pathway (~5-15%) → produces N-acetyl-p-benzoquinone imine (NAPQI), a toxic metabolite, which is detoxified by glutathione (GSH)
4. Elimination Mostly excreted in urine as conjugated metabolites. Elimination half-life (t½): 1-3 hours in healthy individuals. In overdose or liver dysfunction, half-life increases significantly.

Pharmacodynamics (PD) of Paracetamol
1. Mechanism of Action
Inhibits cyclooxygenase (COX) enzymes, mainly COX-2 in the CNS. Unlike NSAIDs, it has minimal peripheral COX inhibition, which explains its lack of significant anti-inflammatory action. Also enhances serotonergic and endocannabinoid pathways, contributing to analgesic and antipyretic effect

. 2. Effects Analgesic (pain relief): Effective in mild to moderate pain, likely by inhibiting prostaglandin synthesis in the brain. Antipyretic (fever reduction): Lowers hypothalamic set-point for body temperature via COX inhibition. Minimal anti-inflammatory action compared to NSAIDs.

3. Toxicity & Overdose Overdose can cause liver damage (hepatotoxicity) due to excessive NAPQI accumulation. Treated with N-acetylcysteine (NAC), which replenishes glutathione stores. Maximum safe dose: 4 g/day in adults (lower in chronic alcohol users or liver disease patients). Uses and Side effects PCM (Paracetamol) is a commonly used medication for pain relief and fever reduction. Here's a breakdown of its uses and possible side effects

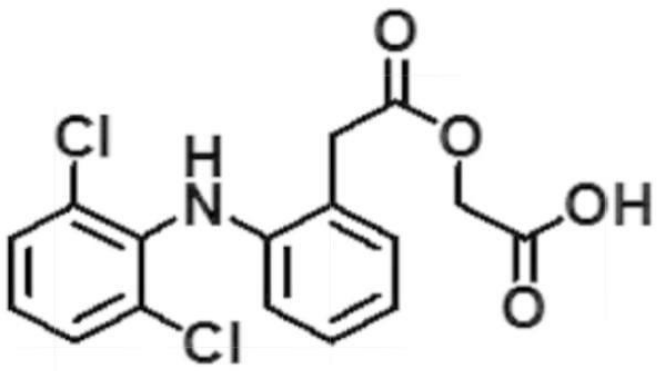
: Uses of Paracetamol (PCM)

1.Pain Relief – Helps alleviate mild to moderate pain, such as headaches, toothaches, menstrual cramps, and muscle pain.
2. Fever Reduction – Lowers body temperature in cases of fever due to infections or illnesses.
3. Post-Vaccination Discomfort – Used to ease mild fever and pain after vaccinations.
4. Arthritis and Joint Pain – Provides relief from pain in conditions like osteoarthritis (but does not reduce inflammation)
5. Cold and Flu Relief – Often combined with other medications in cold and flu treatments to relieve symptom

Side Effects of Paracetamol (PCM) Paracetamol is generally safe when used in the recommended dosage, but possible side effect
1.Common Side Effects (Rare at normal doses) Nausea or vomiting Stomach pain Mild allergic reactions (rash, itching)
2. Serious Side Effects (Usually due to overdose or prolonged use) Liver Damage – High doses can cause severe liver toxicity, leading to liver failure. Kidney Damage – Chronic high-dose use may harm kidney function. Severe Allergic Reaction (Rare) – Symptoms like swelling, difficulty breathing, and skin reactions require immediate medical attention

ACECLOFENAC

Chemical structure The chemical structure of Aceclofenac is C16H13Cl2NO4. It belongs to the aryl acetic acid derivatives class of NSAIDs. Here's a breakdown of its structure:



Aromatic ring:

It has two aromatic rings. One is a benzene ring to which the acetic acid derivative and amino group are attached. The is a chlorinated benzene ring attached to the nitrogen.

Amino group (-NH):

Attached to the chlorinated benzene ring.
Substituents: Two chlorine groups (-Cl) are attached to the benzene ring at the 2&6 position, giving it its unique properties. A large substituted aminophenyl group on the acetic acid moiety.

Mechanism of action .

Inhibition of COX enzymes: These enzymes are responsible for the production of prostaglandins, which are chemicals that mediate pain, inflammation, and fever. Reduction of prostaglandins: By blocking COX enzymes, aceclofenac decreases the levels of prostaglandins in the body. Effects: Analgesic: Reduces pain by lowering prostaglandin-induced sensitivity of nerve endings. Anti-inflammatory: Alleviates inflammation by reducing prostaglandin-mediated swelling and redness. Antipyretic: Lowers fever by acting on the hypothalamus to promote heat dissipation

Pharmacodynamic and Pharmacokinetic effect Pharmacokinetics (ADME)

1. Absorption: Aceclofenac is rapidly and completely absorbed from the gastrointestinal (GI) tract following oral administration. Peak plasma concentration (Cmax) is reached within 1.25-3 hours after oral administration. Food delays absorption but does not significantly affect overall bioavailability.

2. Distribution: Highly protein-bound (~90% to 99%) to plasma proteins, primarily albumin. Volume of distribution (Vd) is moderate (~25 L/kg).
3. Metabolism: Primarily metabolized in the liver via cytochrome P450 (CYP2C9) enzymes. Undergoes hydroxylation and conjugation to form inactive metabolites.
4. Excretion: Eliminated mainly via the kidneys (50% as metabolites,

Pharmacodynamics
1. Mechanism of Action:
Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID). It works by inhibiting cyclooxygenase (primarily COX-2) enzymes, leading to decreased production of prostaglandins (PGs), which are mediators of pain, inflammation.
2. Therapeutic Effects:
Anti-inflammatory: Reduces inflammation in conditions like rheumatoid arthritis, osteoarthritis, and dysmenorrhea. Analgesic (Pain-relief): Used for mild to moderate pain, especially menstrual pain (primary dysmenorrhea). Antipyretic (Fever reduction): Lowers fever by acting on the hypothalamus.
3. Adverse Effects:
GI effects: Gastric irritation, ulcers, bleeding (due to COX-1 inhibition reducing protective gastric PGs). Renal effects: Reduced renal blood flow, risk of acute kidney injury (especially in dehydrated patients). Cardiovascular risks: Increased risk of thrombosis, hypertension, and edema with prolonged use. Hypersensitivity reaction

Uses and Side effects
Uses of Aceclofenac Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID) used primarily for its analgesic, anti-inflammatory, and antipyretic properties.
1. Pain Relief (Analgesic Uses) Primary Dysmenorrhea (Menstrual Pain) – One of the most common uses; it helps reduce menstrual cramps by inhibiting prostaglandin synthesis. Postoperative Pain – Used to relieve pain after minor surgical procedures. Dental Pain – Effective in managing toothaches and post-dental surgery pain. Musculoskeletal Pain – Helps relieve pain from conditions like sprains, strains, and muscle injuries. Headaches and Migraines – Sometimes used for tension headaches and mild migraines.
2. Inflammatory Conditions Rheumatoid Arthritis & Osteoarthritis – Reduces joint inflammation and pain. Gout – Helps in the acute management of gout-related inflammation.
3. Fever Reduction (Antipyretic) Used to lower fever in certain conditions, though other NSAIDs like ibuprofen and paracetamol are more commonly preferred

Side Effects of Aceclofenac Aceclofenac,
like other NSAIDs, can cause a range of side effects, especially with prolonged use or high doses. These can be categorized as common, serious, and rare effects.
1. Common Side Effects
Gastrointestinal (GI) Issues:
Nausea,
vomiting Stomach pain or discomfort Diarrhoea
Indigestion or heartburn Nervous System Effects Dizziness Headache Drowsiness
2. Serious Side Effects (Require medical attention) Gastrointestinal Complications: Stomach ulcers Gastrointestinal bleeding (symptoms: black/tarry stools, vomiting blood) Perforation (rare but life-threatening) Cardiovascular Risks: High blood pressure Increased risk of heart attack or stroke (with prolonged use) Kidney & Liver Issues: Kidney damage (reduced urine output, swelling in feet/hands) Liver toxicity (jaundice, dark urine) Allergic Reactions (Rare but Serious)

➢ COMBINATION OF PARACETAMOL AND ACECLOFENAC
Rationale behind combination: The combination of PCM and Aceclofenac is based on the following principles:
1. Synergistic effect: The two drugs work together to produce a greater analgesic effect than either drug alone. PCM's analgesic effect is enhanced by Aceclofenac's anti-inflammatory properties.
2. Broad-spectrum pain relief: The combination provides relief from various types of painincluding headaches, toothaches, menstrual cramps, and musculoskeletal pain.
3. Faster onset of action: The combination of PCM and Aceclofenac can provide faster pain relief compared to using either drug alone.
4. Reduced side effects: By using a lower dose of each drug, the combination reduces the risk of side effects associated with higher doses of individual drugs.

Formulation:
This combination is commonly formulated in oral dosage forms, especially tablets and suspensions. Below is a general formulation outline

1.Tablet Formulation (Example)

ingredients	Quality

paracetamol	325mg
aceclofenac	100mg
Microcrystalline cellulose	q.s (diluents)
starch	5-10%
polyvinypyrrolidone	2-5%
talc	1-2%
ethanol	q.s(solvent)

Manufacturing Process:

Wet granulation Direct Compression into tables

Optional: film coating for stability and taste masking

1. Sifting: Sift Paracetamol, Aceclofenac, and Microcrystalline Cellulose through a #40 mesh.
2. Dry Mixing: Mix all sifted powders in a blender for 10–15 minutes.
3. Granulation: Prepare a binder solution with PVP K-30 in water or alcohol and add it slowly to the powder blend to form a damp mass.
4. Screening: Pass the damp mass through a #16 mesh to form granules.
5. Drying: Dry the granules at 50–60°C until moisture content is <2%
6. Sizing: Pass the dried granules through a #20 mesh.
7. Lubrication: Add magnesium stearate, talc, and colloidal silicon dioxide. Mix well.
8. Compression: Compress the granules into tablets using a rotary tablet press

Evaluation of Paracetamol (PCM) and Aceclofenac Tablet Dosage Form

1. Pre-Compression Parameters (Granules/Po0wder Blend) Angle of Repose: Assesses flowability of granules; ideal value
2. Post-Compression Parameters (Finished Tablets) Appearance: Tablets should be uniform in color, shape, and free of cracks Weight Variation Test: Ensures uniformity of dose; allowed variation ±5% for tablets ≥250 mg. Hardness Test: Measures tablet strength; typical range 4–8 kg/cm². Thickness: Ensures size uniformity; acceptable variation ±5%. Friability: Checks mechanical resistance; should be

2.Parentral Formulation

Ingredients	**Quantity**
Paracetamol	10mg
Aceclofenac	50mg
Propylene Glycol	0.5-1.0ml
Sodium Hyroxide	q.s. to adjust pH(6-7)
Water for Injectio	q.s. to 2ml

Manufacturing Process (Aseptic Method)

1. Dissolution: Dissolve paracetamol in WFI under stirring. Separately, dissolve aceclofenac in propylene glycol (may require gentle heating).
2. Mixing: Combine both solutions. Adjust pH using sodium hydroxide if needed.
3. Filtration: Pass through a 0.22 µm filter for sterilization.
4. Filling and Sealing: Aseptically fill into sterile ampoules or vials (e.g., 2 mL). Seal under sterile conditions.
5. Quality Control: Test for sterility, pyrogens, assay, pH, clarity

Evaluation of Paracetamol (PCM) and Aceclofenac Parenteral Dosage Form

The evaluation of a combination of Paracetamol (PCM) and Aceclofenac in injection dosage form involves several tests to ensure its quality, safety, and efficacy. Here are some key evaluation parameters

1. Physical Appearance: o Check for clarity, color, and absence of particulate matter in the solution.
2. pH Testing: o Measure the pH of the solution to ensure it falls within the acceptable range for stability and compatibility.
3. Assay of Active Ingredients: o Quantify the amount of Paracetamol and Aceclofenac using methods like High-Performance Liquid Chromatography (HPLC) and UV spectrophotometry to ensure the correct dosage.
4. Sterility Testing: o Ensure the injection is free from microbial contamination.
5. Pyrogen Testing: o Confirm that the formulation does not induce fever when administered.
6. Stability Studies: o Evaluate the stability of the formulation under different storage conditions to determine its shelf life.
7. Compatibility Testing: o Assess the compatibility of the two active ingredients and excipients to ensure no adverse interactions.
8. Viscosity and Osmolarity: o Check these parameters to ensure the formulation is suitable for injection

Recommended Administration:

1. Oral Tablets:

Taken after meals to avoid gastric irritation. With a glass of water.

Dose: Adults: 1 tablet twice or thrice a day depending on severity.
Children: Dose adjusted based on weight (under medical supervision)

2. Injection (Now Banned in India): Previously used in hospital settings for acute pain or high fever. Administered intramuscularly or intravenously by healthcare professionals. Higher risk of side effects like gastrointestinal bleeding, liver, and kidney toxicity led to regulatory ban

PHARMACOLOGICAL EVALUATION
Invitro Studies: In Vitro Studies of Combination of Paracetamol (PCM) and Aceclofenac
Purpose of In Vitro Studies: To evaluate the mechanism of action of PCM + Aceclofenac combination. To check their synergistic, additive, or antagonistic effect on pain and fever-related pathways. To assess the anti-inflammatory potential at cellular and molecular level

Common In Vitro Methods Used:
1. Cyclooxygenase (COX) Enzyme Inhibition Assay Both PCM and Aceclofenac inhibit COX enzymes (especially COX-2), leading to decreased prostaglandin synthesis. In vitro COX inhibition assays use enzyme kits or purified COX enzymes to measure inhibition by the drug combination. Expected Result: Combination may show higher COX-2 inhibition than individual drugs.
2. Prostaglandin (PGE2) Inhibition Assay LPS-induced RAW 264.7 macrophage cells or human monocytes are used. Drugs are added and PGE2 (inflammatory mediator responsible for pain & fever) levels are measured using ELISA. Expected Result: Significant reduction in PGE2 levels with combination treatment.
3. Cytokine Inhibition Assay Evaluate levels of pro-inflammatory cytokines like: Interleukin-1 beta (IL-1β) Interleukin-6 (IL-6) Tumor Necrosis Factor-alpha (TNF-α) Expected Result: The combination is expected to inhibit cytokine release more effectively than monothepy
4. Antioxidant Activity (Free Radical Scavenging) Methods: DPPH assay ABTS assay These assays check the ability of the drug combination to neutralize free radicals, reducing oxidative stress associated with inflammation.
5. Cell Viability and Cytotoxicity Assay MTT Assay is commonly used to evaluate the safety profile of the combination on cell lines. Ensures that the effective anti-inflammatory concentrations are non-toxic
Additional In Vitro Studies (Formulation-Based)
6. Drug Release Study If developing a combination tablet or formulation — in vitro drug release profiles can be studied in simulated gastric or intestinal fluids (pH 1.2 and pH 6.8).
7. Drug Interaction or Compatibility Studies Techniques: FTIR Spectroscopy (Functional group interactions) DSC (Thermal analysis) XRD (Crystalline structure analysis) Ensures there is no chemical incompatibility between PCM and Aceclofenac in combination
Invivo Studies:

In Vivo Studies of Combination of Paracetamol (PCM) and Aceclofenac
Aim:
To evaluate the analgesic, antipyretic, and anti-inflammatory effects of the combination of PCM and Aceclofenac in animal models.

Animal Models Commonly Used: Albino Rats (Wistar strain) Swiss Albino Mice (Healthy animals of either sex, 150-250g for rats or 20-30g for mice

1. Analgesic Activity Studies:
(A) Hot Plate Method (Central Analgesic Activity) Measures reaction time to thermal pain (licking of paw or jumping). Drugs administered orally. Reaction time is measured at intervals (0, 30, 60, 120 min). Expected Result: Combination shows higher pain threshold than individual drugs.
(B) Tail Flick Method Tail of the animal is exposed to a heat source. Time taken to flick the tail is recorded before and after drug administration. Expected Result: Combination increases latency time significantly.
(C) Acetic Acid-Induced Writhing Test (Peripheral Analgesic Activity) Acetic acid (0.6% solution) injected intraperitoneally to induce writhing (pain response). Count the number of writhes after drug treatment. Expected Result: Combination reduces the number of writhes significantly compared to individual drugs.

2. Antipyretic Activity Studies:
Yeast-Induced Pyrexia Model Fever induced in rats using Brewer's Yeast suspension (20%). Rectal temperature measured before and after drug administration at intervals (0, 1, 2, 3 hours). Expected Result: Combination reduces a faster and more prolonged reduction in body temperature compared to individual PCM or Aceclofenac

3.Anti-inflammatory Activity (Optional Study):
Carrageenan-Induced Paw Edema Model Carrageenan is injected into the paw of rats to induce inflammation. Paw volume is measured before and after drug administration using a plethysmometer. Expected Result: Combination reduces paw edema volume significantly.

4.Toxicity and Safety Studies
: Acute Oral Toxicity (OECD guidelines) to determine safe dosage. Observation for mortality or behavioural changes post-drug administration

➢ REGULATORY ASPECTS Role of CDSCO (Central Drugs Standard Control Organization)
CDSCO is the National Regulatory Authority (NRA) for pharmaceuticals and medical devices in India. It works under the Ministry of Health and Family Welfare, Government of India. Key Roles of CDSCO:
1. Regulation of Drugs and Cosmetics Implements Drugs and Cosmetics Act, 1940 and Rules 1945. Regulates import, manufacture, sale, and distribution of drugs across India.
2. Approval of New Drugs & FDCs (Fixed Dose Combinations) Evaluation of safety, efficacy, and quality data of new drugs. Approval of Fixed Dose Combinations (FDCs) like Paracetamol + Aceclofenac after clinical justification.
3. Expert Committee & DTAB Recommendations CDSCO appoints Expert Committees to review: Therapeutic justification Adverse effect Benefit-risk analysis of drug combination
4. Post-Marketing Surveillance & Pharmacovigilance Monitors adverse drug reactions (ADR). Collects safety data of marketed drugs through Pharmacovigilance Programme of India (PvPI).
5. Ban or Restriction of Drugs CDSCO recommends banning of drugs/combinations if: No therapeutic justification. Risk outweighs benefit. The ban is implemented under Section 26A of Drugs and Cosmetics Act, 1940

Guidelines for Approval of PCM and Aceclofenac Combination
1. Regulatory Authority Requirements Mention that approval of fixed-dose combinations (FDCs) must comply with national regulatory bodies like: CDSCO (Central Drugs Standard Control Organization) in India USFDA (United States Food and Drug Administration) in the USA EMA (European Medicines Agency) in Europe
2. Need for Combination Justification You must show scientific evidence that combining PCM and Aceclofenac offers better therapeutic benefits compared to giving them separately. Examples: Faster pain relief, better fever control, reduced dosing frequency.
3. Preclinical Data Animal studies showing safety of the combination. Toxicology studies to check any new side effects when used together
4. Clinical Trial Requirements Phase I: Safety in healthy volunteers. Phase II: Efficacy and dosing studies in patients. Phase III: Large-scale trials to confirm benefits and monitor side effects. (Note: If both drugs are already approved individually, sometimes bioequivalence studies are enough.)
5. Stability and Compatibility Studies Studies proving that Paracetamol and Aceclofenac are stable together in one formulation.
6. Labelling Requirements Proper warnings for possible side effects (like gastric irritation from Aceclofenac). Correct dosage instructions for patients.
7. Post-Marketing Surveillance (Pharmacovigilance) After approval, companies must monitor the drug's safety when sold to the public. Reason for ban : Ban of Paracetamol (PCM) and Aceclofenac Combination What is Banned? The paediatric dosage form of Paracetamol (PCM) [125mg] + Aceclofenac[50mg] combination was banned by the Government of India in August 2004

Who Banned It The ban was imposed by:
Central Government of India Through: Ministry of Health and Family Welfare Based on the recommendations of: Drugs Technical Advisory Board (DTAB) Expert Committee set up by Central Drugs Standard Control Organization (CDSCO) When Was It Banned: Notification Date: 12th August 2024 Official Source: Gazette Notification by Government of India Role of CDSCO in PCM + Aceclofenac Ban: Evaluated safety and efficacy data of PCM + Aceclofenac Injection. Expert Committee found the combination irrational

Reasons for Ban / Restriction:
1. Increased Risk of Adverse Effects: Aceclofenac is associated with: Gastric irritation Peptic ulcer Renal toxicity Hypersensitivity reactions Paracetamol in high doses → Hepatotoxicity. When combined, risk of gastric damage, renal complications, and hepatic stress increases — especially in vulnerable populations (children, elderly, patients with kidney/liver issues).
2. Irrational Fixed Dose Combinations: Some formulations had high doses of both drugs without proper dose justification. Uncontrolled or over-the-counter (OTC) sale led to misuse for minor ailments like mild fever, without monitoring adverse effects.
3. Lack of Significant Therapeutic Benefit Over Individual Drugs: Regulatory authorities argued that combining two antipyretic/analgesic drugs may not provide additional benefit but increases toxicity risk.

4. Guidelines from Expert Committees: In India, the Drugs Technical Advisory Board (DTAB) and Drug Controller General of India (DCGI) reviewed irrational FDCs. Some combinations of PCM + Aceclofenac with higher doses or non-recommended ratios were banned under Section 26A of Drugs and Cosmetics l

Reports of Toxicity — Combination of Paracetamol (PCM) and Aceclofenac

Several clinical studies and pharmacovigilance reports have documented toxicity concerns with the combination of PCM and Aceclofenac, especially in irrational dosing or long-term use.

1. Gastrointestinal (GI) Toxicity Aceclofenac belongs to NSAIDs (Non-steroidal Anti-inflammatory Drugs), which can cause: Gastric irritation Peptic ulcer GI bleeding Nausea, vomiting
2. Hepatotoxicity (Liver Damage) Paracetamol is safe in therapeutic doses but can cause liver toxicity in overdose. Reported Effects: Elevated liver enzymes (SGOT, SGPT). Liver failure reported in patients using high doses or in combination with other hepatotoxic drugs.
3. Renal Toxicity (Kidney Damage) Both drugs have been associated with renal issues: Acute kidney injury (AKI) Nephrotoxicity Electrolyte imbalance Mechanism: NSAIDs (Aceclofenac) inhibit prostaglandin synthesis → reduces renal blood flow → kidney damage especially in dehydrated patients or elderly.
4. Hypersensitivity Reactions Skin rashes Allergic reactions Bronchospasm (especially in asthmatic patients

➢ REGULATORY ACTION AND GLOBAL STATUS

: WHO and US FDA Decision on PCM + Aceclofenac Combination Ban

1. World Health Organization (WHO) Status: WHO has not issued any global ban specifically on the combination of Paracetamol (PCM) and Aceclofenac. However, WHO emphasizes rational use of Fixed Dose Combinations (FDCs) — meaning combinations must be justified for safety and efficacy. WHO recommends caution in the use of NSAIDs like Aceclofenac, especially in children and patients with kidney or liver disease. Note: WHO includes both drugs in its Model List of Essential Medicines individually, but not as a fixed-dose combination (FDC).
2. US FDA (Food and Drug Administration) Status: In the USA, Paracetamol (Acetaminophen) and Aceclofenac are approved as individual drugs for specific indications. The combination of PCM + Aceclofenac is not approved by the US FDA as a fixed-dose combination (FDC). No specific ban was required because the combination was never approved for marketing in the US

Reasons:

Lack of sufficient clinical evidence for additional benefit from the combination over monotherapy. Safety concerns due to risk of: Hepatotoxicity (from PCM in high doses)

Gastrointestinal bleeding and renal toxicity (from Aceclofenac) Pharmacovigilance Strengthening for Banned Combination of PCM and Aceclofenac (Injection)

Pharmacovigilance plays a crucial role in monitoring and strengthening drug safety after the ban of the dosage form of PCM (Paracetamol) and Aceclofenac combination.

Key Measures for Strengthening Pharmacovigilance

1. Adverse Drug Reaction (ADR) Monitoring Mandatory reporting of ADRs related to PCM + Aceclofenac to PvPI (Pharmacovigilance Programme of India). Focus on adverse effects like: Hepatotoxicity (liver damage) Gastrointestinal bleeding Renal impairment Hypersensitivity reactions
2. Awareness Among Physicians & Pharmacists Circulation of safety alerts and regulatory updates by CDSCO regarding the ban. Training programs for healthcare professionals on rational prescribing and reporting ADRs.
3. Strengthening PvPI Centres Encouraging hospitals and medical colleges to report cases of irrational use or side effects of banned combinations. Surveillance of misuse of injectable formulations in rural or unregulated sectors.
4. Patient Education & Counselling Educating patients about the ban of injection form. Promoting the use of approved oral dosage forms only. Warning against self-medication or OTC use of banned combinations.
5. Regulatory Surveillance CDSCO and State Drug Control Authorities to conduct regular inspections in the market to prevent the sale of banned formulation
6. Global Collaboration Coordination with WHO drug safety databases (VigiBase) for international data on adverse events related to PCM + Aceclofenac combination. Learning from regulatory actions in other countries.

Patient Safety Measures Precautions:

1. Always take after food to minimize gastric irritation.
2. Use only for short-term therapy (3-5 days).
3. Monitor for signs of: Stomach pain Nausea or vomiting Dark urine (liver damage) Allergic reaction (rash, swelling, breathing difficulty).
4. Maintain adequate hydration during treatment
5. Avoid alcohol consumption (increases liver toxicity risk).
6. Do not take additional NSAIDs (ibuprofen, diclofenac) with this combination

Contraindications

1. History of peptic ulcer or gastrointestinal bleeding.
2. Known hypersensitivity or allergy to Paracetamol or Aceclofenac.
3. Severe liver impairment or hepatic disease.
4. Severe renal (kidney) impairment or kidney disease.
5. History of bronchial asthma induced by NSAIDs.
6. Children below 6 months (without appropriate pediatric dosing).
7. Patients with cardiovascular disorders like uncontrolled hypertension or heart fail

Case Study

Title: Development of severe hepatotoxicity due to Paracetamol and Aceclofenac Combination

Patient Details:

Name: Ms. suman

Age: 58 years Gender: Female

Occupation: Housewife

Medical History: Osteoarthritis of the knees, well-controlled hypertension.No prior history of liver disease or heavy alcohol consumption .

Presenting Complaint:

The patient presented to the emergency department with complaints of:

• Progressive fatigue and weakness for the past two weeks.
• Nausea and vomiting for the past three days
• Yellowing of the skin and eyes (Jaundice) noticed since yesterday.
• Right upper quadrant abdominal pain

Clinical Findings

The patient visited the hospital after 1 day due to worsening symptoms. Examination revealed: Scleral Icterus and jaundice The abdomen was tender in the right upper quadrant No signs of gastrointestinal bleeding

Laboratory Investigations:

• Liver Function Tests
• Renal Function Tests
• Viral Heoatitis Serology

Diagnosis:

Adverse Drug Reaction (ADR) due to Paracetamol and Aceclofenac leading to: Injection site reaction (local abscess) Gastritis Early liver stress (Hepatotoxicity)

Treatment Given

: Immediate discontinuation of Paracetamol + Aceclofenac combination Supportive care including i.v. fluids, monitoring of liver functions Hepatoprotective agents Monitoring for signs of liver failure

Outcome:

The patient recovered fully after several days of treatment with supportive care. The doctors instructed to avoid Paracetamol and NSAIDS without medical advice

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Discussion

This hypothetical case illustrates the potential for significant toxicity, in this instance , severe hepatotoxicity , associated with the prolonged use of the paracetamol and aceclofenac combination.while both drugs can have individual risks, their combination, especially in a fixed dose without individual dose adjustments and prolonged use , may increase the severity of adverse events in some patients.

➢ Conclusion:

The combination of PCM & Aceclofenac can be a valuable option for managing pain and inflammation, offering potentially faster and more effective relief than aceclofenac alone. However like all medication, its essential to use it responsibly, adhering to the prescribed dosage and duration, and being aware of potential side effects and contraindications. Individuals with underlying health conditions or those taking other medication should consult their doctor before using this combination to ensure its safety, suitability for their specifical needs

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