# Off label use of Drugs

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# OVERVIEW



- Definition
- Historical aspects
- Examples
- Reasons behind off label use of drug
- Legal vulnerability of physicians
- Ethical issues
- Regulations
- Conclusion

# DEFINITION

- When a drug is used in a way that is **different from what is described in the approved drug label**, it is said to be an "**off-label**" use.



✓Different indication

✓Different dose

✓Different duration

✓Different patient group

✓Different route of administration

## Example

- Drug X is approved for migraine **prophylaxis** at a dosage of **500 mg**, to be administered for **15** days in **adult** patients via the **subcutaneous route**.

- ✓ Migraine **treatment-** different indication
- ✓ **1000** mg - different dose
- ✓ **30** days- different duration
- ✓ **Pediatric** age- different patient group
- ✓ **Intramuscular-** different route of administration

# HISTORICAL ASPECTS

- **Pfizer incident**

  - Pfizer marketed four drugs (**valdecoxib**, **pregabalin**, **linezolid**, and **ziprasidone**) for off-label uses.

  - As a result, Pfizer has to pay a $2.3 billion fine, the largest healthcare fraud settlement in U.S. history.

- **Sun Pharma incident:**

  - Sun Pharmaceuticals promoted **Letrozole**, which is approved for breast cancer in postmenopausal women, for **off-label use in treating infertility.**

- As a result, in 2003, the Ministry of Health and Family Welfare (MoHFW):

- ✓ Issued a warning to the company to stop this promotional activity.
- ✓ Destroyed all promotional materials claiming Letrozole's off-label use.
- ✓ Advised states that Letrozole is not approved for infertility treatment.
- ✓ In 2011, under Section 26A of the Drug & Cosmetic Act, the government suspended the manufacturing of Letrozole for ovulation induction.

## Thalidomide: From Ban to Approval

- **1962:** Thalidomide, originally approved for insomnia, was banned by WHO due to severe side effects.

- **1964:** Dr. Jacob Sheskin accidentally discovered thalidomide's antileprosy effects when he gave it to a patient with ENL(erythema nodosum leprosum) for its sleep-inducing properties.

- **1997:** After placebo-controlled trials by Celgene, the FDA approved thalidomide for treating ENL.

## Dr Gleason incident

- Dr. Gleason prescribed the narcolepsy drug **Xyrem (sodium oxybate)** off-label to treat major depression and fibromyalgia in USA.

- In 2003, the drug's manufacturer asked him to share his experiences with other doctors at promotional talks and medical education conferences.

- Three years later, Dr. Gleason was arrested and charged with conspiracy to illegally market the drug.

## Michael Jackson incident:

- Dr. Conrad Murray was found guilty of involuntary manslaughter in 2011 for giving Michael Jackson a fatal dose of **propofol** leading to Jackson's death on June 25, 2009.

- Murray had been giving Jackson propofol to help him sleep, which is a dangerous off-label use of the drug, especially outside of a hospital.

## Mediator scandal:

- The Mediator off-label scandal in France involves the diabetes drug **Mediator (benfluorex),** which was widely used off-label for weight loss.

- **Drug Approval**: Mediator was approved in France in 1976 to treat diabetes by controlling blood sugar levels.

- **Off-Label Use**: Many doctors prescribed Mediator off-label as a weight loss aid, even though it wasn’t intended for that purpose.

- **Health Risks**: Over time, evidence showed that Mediator could cause serious health problems, including heart valve damage and lung issues.

# Current Off-Label Uses of Established Medications

| Drug | Off label use |
| --- | --- |
| Phenobarbital | Hyperbillirubinemia |
| Clonidine | Opioid & Alcohol withdrawl |
| Indomethacin | Preterm labour |
| Losartan | Gout |
| Ketorolac | Migraine, Pericarditis |
| Terbutaline | Uterine relaxant |
| Levonorgestrel IUD | Endometriosis , Menorrhagia |
| Spironolactone | Female pattern alopecia |
| Tranexamic acid | Melasma |
| Minoxidil | Androgenic alopecia |
| Finasteride | Female pattern hair loss |

| Drug | Off label use |
| --- | --- |
| Calcipotriene | Vitiligo |
| Leuprolide(GnRH agonist) | Preserve follicles in women undergoing therapy with cytotoxic drug |
| Misoprostol | Cervical ripening<br>Postpartum haemorrhage |
| Cidofovir | Anogenital warts by HPV |
| Methotrexate | Multiple inflammatory dermatoses |
| Bupropion | Obesity |
| Intravenous IG | Toxic epidermal necrolysis |
| Azathioprine | Pemphigus vulgaris |
| Mycophenolate Mofetil | Systemic lupus erythematous |

| Drug | Off label use |
|---|---|
| Magnesium sulphate | Premature labor(>5-7 days) |
| Sertraline | Premature ejaculation |
| Topiramate | Bipolar disorder |
| Propranolol | Performance anxiety |
| Sildenafil | Female sexual arousal disorder |
| Aspirin | Recurrent miscarraige<br>Coronary disease prophylaxis in high-risk diabetic patients. |
| Celecoxib | Gout |
| Quetiapine | Insomnia |
| Succimer(Dimercaptosuccinic acid) | Mercury and Arsenic poisioning |
| Metformin | Polycystic ovarian syndrome |
| Thalidomide | Cutaneous lupus erythematous |
| Cetrorelix(GnRH antagonist) | Endometriosis & Fibroids |

| Drug | Off label use |
|---|---|
| Morphine | Pain in children |
| Fluoxetine | Hot flushes |
| Prazosin | Post-traumatic stress disorder |
| Gabapentin | Neuropathic pain |
| Clonidine | Attention deficit hyperactivity disorder |
| Topiramate | Migraine |
| Letrozole | Ovulation induction |
| Propranolol | Migraine |
| Semaglutide | Weight loss |
| Ropinirole | Restless leg syndrome |

# TYPES OF OFF LABEL USE

- **Dose:**
  - Example: 150-200 mg dose of **sildenafil** is used off-label for erectile dysfunction.

- **Age:**
  - Example: **Quetiapine** is used in the pediatric population(<10 year) for bipolar disorder.

- **Indication:**
  - Example: **Sertraline** is used for premature ejaculation.

- **Route:**
  - Example: **Tacrolimus** originally approved for oral route but used sublingually in a patient not able to take orally.

# REASON BEHIND OFF LABEL USE

- A medication may not have been studied and approved for a specific population (e.g., pediatric, geriatric, or pregnant patients).
- A life-threatening or terminal medical condition may motivate a health care professional to give any treatment that is logical and available, whether approved by the FDA or not.
- If one medication from a class of drugs has FDA approval, physicians commonly use other medications in the same class without specific FDA approval for that use for the same indication.
- If the pathologic or physiologic features of two conditions are similar, a physician may use a medication for one of these conditions for both.

# FREQUENCY OF OFF-LABEL USE



- Approximately **21% to 32%** of all prescriptions are off-label, with the highest use in psychiatry and oncology.
- In oncology, one-third of cancer drug administrations are off-label, and over half of cancer patients receive at least one off-label drug.
- Off-label use is also quite common in pediatric, geriatric, and pregnant populations.

# WHY MEDICINES MAY REMAIN OFF-LABEL?

- Drug sponsors must apply for FDA approval for new uses.
- Pharmaceutical companies may avoid seeking approval due to:
  - ✓High costs
  - ✓Lengthy processes
- The FDA approval process often lags behind therapeutic advances.
- After patent expiration, companies are less inclined to invest in studies for new uses of generic drugs.
- New uses might only benefit a small number of patients, making approval investments unprofitable.

# OFF LABEL / ON LABEL

- **On-Label Use:** Drugs approved for specific conditions have undergone rigorous testing and regulatory review to ensure their benefits outweigh the risks for that particular use.

- **Off-Label Use:** Using drugs for conditions not specifically approved carries uncertain risks and benefits.

- **Safety Considerations:**

  - **Indication:** A drug may be safe for one condition but not for another (e.g., **Amiodarone** is approved for ventricular fibrillation but not for atrial fibrillation).

- **Dose:**
  - ✓ Safe at low doses
  - ✓ Potentially harmful at higher doses

- **Duration:**
  - ✓ Safe for short-term use
  - ✓ Dangerous for long-term use

- **Age:**
  - ✓ Safe for some age groups
  - ✓ Not safe for other age groups

- **Route:**
  - ✓ Safe when administered one way
  - ✓ Not safe when administered another way

# POTENTIAL BENEFITS OF OFF-LABEL USE

- **Innovation in Treatment:** Off-label use can lead to discovering new, effective treatments for conditions that lack approved options.
- **Personalized Medicine:** It allows doctors to tailor treatments to individual patient needs, potentially improving outcomes.
- **Cost-Effective Solutions:** Can provide more affordable alternatives if the off-label drug is cheaper than the approved treatments.
- It is sometimes the only alternative in special circumstances (serious/ **orphan diseases**, **compassionate use** when no other treatment is available, emergency scenario like **pandemic**, etc.) .

# OFF-LABEL USE AND DRUG REPURPOSING

- Off-label use, especially through academic trials, can be crucial in discovering new therapeutic uses for existing generic drugs—a process known as **drug repurposing**. Here's why it's beneficial:

- ✓ **Limited Commercial Incentive:** Pharmaceutical companies often lack financial motivation to invest in repurposing generic drugs since these drugs are no longer patent-protected, reducing the potential for significant profit.

- ✓ **Academic Research:** Universities and research institutions can conduct trials on off-label uses, driven by scientific curiosity and public health needs rather than profit. This research can uncover new, valuable uses for established drugs.

- **Examples of Success:**

- **Minoxidil:**
- ✓ **Original Use:** Treatment for high blood pressure
- ✓ **Repurposed Use:** Treatment for hair loss (topical form)

- ✓ **Public Health Impact:** Drug repurposing can offer effective treatments for conditions with limited or no current options, benefiting patients and healthcare systems.

# LEGAL VULNERABILITY OF PHYSICIANS

- Physicians may face legal challenges due to adverse reactions from off-label drug use.
- Lawsuits often cite **inadequate informed consent**, and **medical negligence**.
- In India, medical practice is governed by the Professional Conduct, Etiquette, and Ethics Regulations (2002), but there are no specific rules regarding off-label prescribing.

❖ **To mitigate liability, physicians should:**

✓ Inform patients about off-label use.

- ✓ Ensure patient benefit is the primary goal.
- ✓ Decisions should be based on expert medical opinions.
- ✓ Use reputable scientific literature support.
- ✓ Seek support from colleagues.

# CAN A DOCTOR BE SUED IF OFF LABEL CAUSES HARM TO THE PATIENT?



- Off-label prescribing depends on the case. If scientifically supported, it may not be an offense.

- However, if better alternatives exist or the scientific rationale is weak, a lawsuit is possible:

✓ **Criminal Liability:** Sections **304A**, **337**, **338** of IPC

✓ **Monetary/Civil Liability:** Consumer Protection Act 1986

✓ **Disciplinary Action:** Professional Conduct, Etiquette, and Ethics Regulations, 2002 (Indian Medical Council Act, 1956)

# IS PROMOTION OF OFF LABEL USE- BY A PHARMACEUTICAL COMPANY ILLEGAL?



- Off-label marketing by pharmaceutical companies are regarded as a violation of law in India, and it is an offence under the Drug and Magic Remedies (objectionable advertisements) Act, 1954.

# ETHICAL ISSUES: PATIENT'S CONSENT

- **Where there is high-quality evidence supporting off-label use:**

- ✓ **Explain the Reason**: Discuss why the off-label medication is being recommended.
- ✓ **Discuss Alternatives**: Outline alternative therapies available.
- ✓ **Review Side Effects**: Inform the patient about possible side effects.
- ✓ **Address Uncertainties**: Provide additional information about any uncertainties due to the off-label use.
- ✓ **Address Patient Concerns**: Offer extra information if the patient has specific concerns.

## Where there is no high-quality evidence supporting off-label use:

- **Hospital Approval**: Ensure the hospital drug committee has approved its use for individual cases.
- **Informed Consent**: Obtain documented written consent from the patient.
- **Explain the Situation**: Clearly inform the patient about the off-label use, the lack of high-quality evidence, and why it's being considered.
- **Discuss Risks and Alternatives**: Explain potential risks and available alternatives.

## Where a hospital administers a medicine imported by a patient for personal use:

- **Informed Consent**: Obtain documented written consent from the patient.
- **Explain the Risks**: Inform the patient about the potential risks since the medicine hasn't gone through the usual evaluation and approval processes.
- **Patient's Own Supply**: If the patient uses their own imported medicine against medical advice, ensure they acknowledge understanding the risks.
- **Record Keeping**: Hospital staff must record the medical advice given and the patient's acknowledgment in writing.

# REGULATORY FRAMEWORK FOR DRUGS IN INDIA



- **Approval and Regulation:**

  - The Drug Controller General of India (DCGI) approves new drugs.
  - Clear guidelines on off-label drug use are not provided by DCGI.

- **Legal Restrictions:**

  - **Prescribing:** Off-label prescribing is illegal under amendments to the Indian Medical Council Act.

  - **Marketing:** Off-label marketing by pharmaceutical companies violates the Drug and Magic Remedies (Objectionable Advertisements) Act, 1954.

## Professional and Public Opinion:

- **Indian Medical Association:** Supports off-label prescribing but recognizes the lack of specific regulations.

- **Consultants' Concerns:** Worry that allowing off-label prescribing may negatively impact due to patient ignorance and pharmaceutical company influence.

## ❖ Exceptions for Life-Saving Drugs:

### ➢ Import by Individuals:

- Small quantities of otherwise prohibited drugs can be imported for personal use under specific conditions.

### ➢ Import by Government Hospitals/Institutions:

- Applications can be made to import new drugs not approved in India but approved in their country of origin for patients with life-threatening conditions or unmet medical needs.

### ➢ Emergency Use During Disasters:

- Under the National Ethical Guidelines, there are provisions for monitored emergency use of unregistered and experimental interventions during humanitarian emergencies.

## Proposed Amendment (June 2020):

- The Ministry of Health and Family Welfare proposed an amendment to allow hospitals/medical institutions to import unapproved new drugs for compassionate use.

- This applies to:
  - Life-threatening diseases
  - Diseases causing serious permanent disability
  - Diseases requiring therapy for unmet medical needs
  - Drugs under Phase-III clinical trials in India or other countries

- This amendment is still in the draft stage.

# UNITED STATES



- In the United States, doctors can prescribe approved medications for uses other than their specific FDA-approved purposes.

- **Drug Marketing**: When a pharmaceutical company markets a drug, they can only promote it for specific uses that the FDA has approved. These approved uses are based on evidence showing the drug is both safe and effective for those specific conditions.

- **Physicians**: Can prescribe drugs for any use they believe is safe and effective, not just the FDA-approved uses.

# UNITED KINGDOM



- In the UK, doctors can prescribe medications off-label. According to the British General Medical Council:

- **Better Option**: The off-label prescription must better serve the patient's needs than other alternatives.

- **Support**: There must be evidence or experience showing that the off-label use is safe and effective.

# ROLE OF REGULATING AGENCIES

- **Post-Marketing Surveillance**

- After a drug is approved, agencies like the FDA (Food and Drug Administration) in the U.S. and the EMA (European Medicines Agency) in Europe keep monitoring it. They make sure the drug remains safe and effective even after it's available for public use.

- **Drug Utilization Studies**

- These studies help agencies understand how drugs are actually being used by looking at electronic health records. They show how often off-label prescribing occurs and help identify any potential safety issues.

## Signal Detection and Safety Monitoring

- Agencies use the data from drug companies to keep an eye on drug safety. They look for any warning signs that might indicate a problem with a drug. This helps ensure the drug is safe for continued use.

## Adverse Event Reporting

- Agencies also monitor reports of adverse events.It doesn’t matter if the drug was used off-label; if it caused a adverse reaction, it must be reported. This helps to protect patient safety.

# HOW CAN WE REGULATE OFF LABEL USE?



- **TEMPORARY RECOMMENDATION FOR USE FRAMEWORK (TRU)**

- Implemented in France in 2012 in response to Mediator® off label use scandal.

- Aims to control irrational off-label drug use

Signal of off label use of a medicine

↓

No alternative approved medicine + Benefit > Risk

↓

Pharmaceutical company and the ANSM enter into formal contract [ANSM is French Agency of Medicine and Health Product Safety]

↓

Periodic summary reports ( for safety and efficacy) submitted to ANSM after 3 years

↙ Risk found or deviation from protocol

↓

TRU is withdrawn

↘ Benefit > Risk

↓

TRU can be renewed

# NEED OF THE HOUR

- In balancing innovation with evidence-based medicine, the following are crucial:

- **Rational Prescribing**: Use off-label medications only when appropriate, supported by scientific evidence, and when other approved treatments have failed. Ensure benefits outweigh risks and obtain informed consent from the patient or legal guardian.

- **Evaluation of Scientific Evidence**: Before prescribing, thoroughly review available medical literature on the drug, ensuring its relevance and reliability. Conduct extensive literature searches and confirm the level of evidence.

- **Safety Monitoring**: Implement methods like spontaneous adverse drug reaction (ADR) reporting and observational epidemiological studies to identify, analyze, and monitor ADRs associated with off-label drug use.

# CONCLUSION

- Off-label prescribing is widespread globally, allowing doctors to explore new treatment options based on emerging evidence.
- Physicians legally prescribe approved drugs for off-label uses, sometimes without sufficient evidence beyond medical practice.
- Patient requests for new treatments after standard options fail often drive off-label use.
- Concerns arise regarding safety and effectiveness due to lack of proper risk-benefit analysis by regulatory agencies.

- Regulatory approval demands substantial evidence of efficacy and safety for specific indications, but clarity on off-label regulations is lacking.
- Financial incentives make it impractical to expect pharmaceutical companies to restrict off-label promotion.
- Off-label use can be beneficial for some patients but may expose them to risks or ineffective medication.
- Urgent need for guidance to encourage proper off-label use through scientifically valid information distribution by pharmaceutical companies.

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Thank You!