Overview of regulatory systems and technology for tracking counterfeit, adulterated and sub-stranded medications with the recommendation in Indian regulatory systems

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ABSTRACT

Drugs maintain wellness, prevent illness, treat disease, stop epidemics, and save lives. Fake, adulterated, and substandard medications are the main obstacle to this goal. Falsified drugs contain unclean, filthy, or rotting substances. In India, medication is "Not of Standard Quality" if it doesn't meet requirements. Fake or counterfeit pharmaceuticals threaten the industry's reputation and public health. Anyone promoting Substandard/ Spurious/ Falsely-labelled/ Falsified/ Counterfeit Medical Products on the market can have their licence suspended. Mashelkar Committee suggests regulatory frameworks to eliminate fake and inferior medications. The committee considers amending the Drugs and Cosmetics Act to punish fake drug sellers. The government has changed how whistleblowers are rewarded. This initiative includes informants and officials. Several anti-counterfeit medicine technologies can track real and fake drugs. The Broadband Acoustic Resonance Dissolution Spectroscopy test uses a dissolution-based method to identify fake and real medication products using an audio spectrum.

Keywords: Spurious drug, Sub-stranded, Counterfeit, Adulterated, Falsified

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INTRODUCTION

Pharmaceuticals and drugs are essential for maintaining health, preventing disease, curing diseases, averting epidemics, and saving lives. They must be secure, effective, and of the proper standard to accomplish this goal.The global threat of spurious, adulterated, and non-standard quality medications has emerged as the main barrier to reaching this goal. Though the issue of non-standard quality pharmaceuticals has drawn the attention of the public and government organisations, it has not yet been adequately resolved.[1]

In India, the provisions of the Drugs and Cosmetics Act, 1940 and Rules, 1945 are implemented by the State Drugs Control Departments (SDCD) under each State Government and the Central Drugs Standards Control Organization (CDSCO) under the Central Government. Due to the simultaneous setup of the drug regulation mechanism in India, the system has been crippled and is unable to provide patients with high-quality medications due to the limitation and overlapping functions of such a system.[2][3]

It is quite essential to discuss the problem of non-standard quality pharmaceuticals in India since it has reached alarming levels.Although the government has made an effort to strengthen the regulatory structure, it seems to be moving slow and is insufficient. For instance, the Mashelkar Committee Report from 2003 is an example. However, the suggestions from these assessments have not been fully put into action.[4]

The whistleblower scheme amended by CDSCO and their rewarding guidelines is an initiative for the eradication of SSFFC/NSQ drugs in India. Various sub-stranded drug tracking technologies and tests like BARDS are in use to differentiate false and genuine drug products.[5]

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Spurious drug:

According to WHO, spurious pharmaceuticals are purposefully and unlawfully mislabeled and created to misinform and deceive consumers (patients). The manufacturer's name or content is based on fast-selling branded or generic drugs. Spurious medications may or may not contain the label.[6]

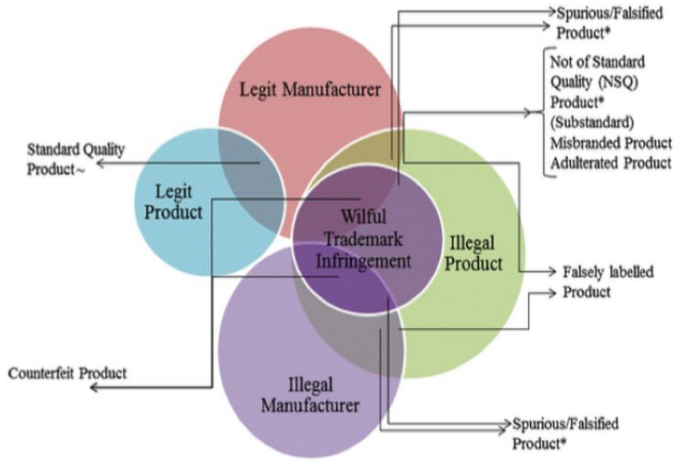
Adulterated drug

According to Section 17-A of the following Provisions, A drug is adulterated if it (a) "consists in whole or in part of any filthy, putrid, or decomposed substance; (b) has been manufactured, packaged, or kept under unsanitary conditions that may have contaminated it with filth or made it injurious to health; or (c) if its container is made of any dangerous or harmful substance.[7]

Counterfeit medicines

The word "counterfeit medicines," which has numerous definitions, is used most frequently on a global scale. Medicines that have been purposefully and fraudulently mislabeled about identity and/or source are known as spurious/ substandard/ falsely labelled/ falsified/ counterfeit (SSFFC) medications. All SSFFC medications are prohibited. They may cause the treatment to fail or possibly cause death. The stated Act does not employ the word "counterfeit," which is widely used around the world, in India. The word "spurious" is used.[8][5]

Figure 1: Depiction of SSFFC terms and terms used in the Drugs & Cosmetic Act based on documented definitions in iterations reproduced over the years



NSQ – Not of Standard Quality

Problems with the quality of drugs in the nation have been recognised by the "Survey of Extent of Problems of Spurious and Not of Standard Quality (NSQ) Drugs in the Country." If a medicine does not adhere to the requirements listed in the Second Schedule2 of the aforementioned Act, it is considered to be "Not of Standard Quality" in India. Not of Standard Quality (herein referred to as NSQ) pharmaceuticals, also known as substandard or poor quality drugs, pose a pandemic hazard and are a significant source of worry for national and international health systems.[7]

As part of their routine inspections of locations that produce or distribute drugs, the officers take drug samples as specified in the aforementioned Act and transmit them to the Government Drugs Testing Laboratories for analysis. These labs examine the samples and generate reports following the guidelines outlined in the following Provisions, proclaiming a drug sample to be of Standard Quality or Not of Standard Quality, as the case

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may be, and outlining the parameters examined and the justifications for doing so.[3]

After a medicine is designated as NSQ, the recall process and other legal procedures must be started. Effective recall of the medications listed as NSQ is essential.

Substandard/ Spurious/ Falsely-labelled/ Falsified/ Counterfeit Medical Products (SSFFC)

The World Health Assembly (WHA) recommendedconcerted worldwide action to limit SSFFC medications as early as 1988. [9]

In the Americas, the WHO guidelines to prevent medication counterfeiting were presented at the II Pan American Conference on Drug Regulatory Harmonization (1999) and it was concluded that [10]:

1. Most countries in the region have a problem with falsified medicine, and some have taken strong measures to reduce it;[10][11]
2. The country can use the guidelines for developing the fight against fake medications as a tool;[11]
3. Most nations lack modern legislation that would enable them to confront this crime and impose severe penalties;[10]
4. Health officials must work with the police, the judiciary, producers, and distributors to properly address the issue. In some nations, the unrestrained expansion of pharmacies and distribution networks may have reduced the prevalence of this crime.[11]

Guidelines for responding to fake or sub-standard standard drug samples have been established in light of the severe penalties under The Drugs and Cosmetics (Amendment) Act of 2008.

"The Drugs and Cosmetics (Amendment) Act, 2008, which was approved by the Parliament on December 5, 2008, establishes severe penalties for offences involving the production of falsified or contaminated drugs that seriously endanger public health.[6]

The following are the main categories of reports that are not of standard quality:-

Category A

(Spurious and Adulterated Drugs)

Spurious or false medication products are made to seem like other drugs, especially popular ones, to deceive consumers and profit from their popularity. The active components may or may not be present in the product. False medications are mostly produced by illegal, anti-social actors, though occasionally legitimate producers may also be involved. Drugs that are determined to be contaminated with filth or to contain an adulterant or replacement product that endangers human health are considered adulterated.

The confidence of domestic and foreign customers has been impacted by reports of the availability of spurious drugs in the nation. The problem's emotional state must be treated firmly and in coordination with other agencies.[7]

Category B

(Sub-stranded drugs)

Drugs made by authorized manufacturers but said to have serious defects that damage quality Such defects might result from mistakes or non-GMP manufacturing procedures.

The following may broadly describe these defects:

- Less than 70% of the permitted active component concentrations are in thermolabile products and 5% in thermo stable products.
- Non-disintegrating tablets or capsules.

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- Tablets/capsules that fail the dissolving test and have less than 70% for thermo labile goods and less than 5% for thermo-stable products.
- Fungal-growing liquids
- Parental preparations that failed pyrogen/endotoxin tests or were toxic.
- Toxic, sterile, potent, or moist vaccines.
- Harmful adulterants.[7]

Category C
(Minor defects)

Due to quality imbalances, licensed manufacturers' medications were substandard. Insufficient pre-formulation development studies, absence of process controls, or improper storage or transportation might cause such problems. Examples of some of these faults include the following:

- Tablets with cracks or breaks.
- Spots and discolouration covering are present.
- Emulsion cracking.
- Liquid preparations that are clear but have sediment.
- A change in the formulation's colour.
- Little changes to the net's content.
- Formulations with weight fluctuation issues.
- Formulations that did not pass the colour test.
- Isolated instances of alien material presence.
- Nomenclature mistakes, Rx, NRx, XRx, Red Line, Schedule H, and other labelling errors are included. Safety, colour, etc.[7]

Guidelines

State Drug Control Organizations should adopt these principles for uniform Drug and Cosmetics Act compliance. State regulatory agencies must execute the new regulations. To effectively use the law, each state needs Standard Operative Procedures to examine and process Act violations. Internal checks and balances should protect law-abiding drug manufacturers and sellers. While criminal intent or gross negligence should lead to serious defects, minor quality variations by registered manufacturers should be handled structurally.[7]

1. Unlicensed makers or distributors that market spurious or counterfeit drugs must be investigated immediately and section 36 AC of the Act must be applied, as they are cognizable and non-bailable offences.[7]
2. If a licenced manufacturer developed and/or marketed counterfeit drugs utilising licenced premises, the case must be investigated with the same vigour as an unlicensed producer. Literature reviews should include manufacturer actions.[7]
3. Drugs If a licenced manufacturer developed and/or marketed counterfeit drugs utilising licenced facilities, the case must be pursued with the same vigour as an unlicensed producer. Literature reviews should include other manufacturer activities produced by a licenced manufacturer under a valid manufacturing licence and proven to be substandard, prosecution should be applied sparingly when administrative procedures like suspension or revocation of licences or compounding of offences would not meet justice's objectives.[6]
4. Administrative measures such as suspension/cancellation or compounding of offences may be applied for unsatisfactory reports due to small deviations from defined

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standards or violations of other sections of chapter IV of the Act. When the steps don't bring justice, a lawsuit may be brought.[6]

5. Section 36 AC makes Act offences guilty of the offence and non-bailable to catch anti-social elements making false or defective pharmaceuticals. Only when offenders can be properly investigated should the clause be enforced.[6]

Dr Mashelkar Committee report

The Indian Ministry of Health and Family Welfare established an Expert Committee on January 27, 2003, chaired by CSIR Director General Dr.R.A. Mashelkar, to investigate drug regulatory issues, including fraudulent pharmaceuticals.[4]The Expert Committee's guidelines were as follows.

- Encourage a new drug regulating system that includes a National Drug Authority.
- Strengthen the States and the Centre's drug regulation infrastructure.
- Evaluate the counterfeit and inferior drug situation and recommend solutions.
- Amend the 1940 Drugs and Cosmetics Act and related legal processes.
- Make proposals to the pharmaceutical industry and pharmacy association to prevent fake drugs.
- Think about and advise on any other problem related to the aforementioned.
- Create implementation plans for all suggested actions.

Executive Summary

1. Spurious/counterfeit/substandard drugs are an issue. The Indian Supreme Court, National Human Rights Commission, and parliamentarians want better drug control. The Drugs and Cosmetics Act hasn't been altered since its inception, but the Rules have. The Indian government has constituted various advisory bodies. The government partially implemented these recommendations, but problems remain.
2. The Indian government nominated Dr R.A. Mashelkar to analyse fake medications. The group was instructed to recommend and implement a solution. Scientists, lawyers, and police commissioners are on the committee. Trade, consumer, and professional organisations are members. Health Secretary (India).
3. The committee looked at former committees' recommendations, progress made, and implementation difficulties.[12]
4. Despite being in place for 56 years, several states have weak drug laws. Non-uniform legal analysis and application and varying regulatory official ability caused this low performance.[12]
5. The Committee stated that difficulties in the country's regulatory system were attributable to poor drug control infrastructure at the State and Central levels, insufficient testing facilities, a scarcity of drug inspectors, non-uniform enforcement, a lack of particularly educated officials for certain regulatory sectors, no data bank, and misleading information.[13]
6. The Committee recommends modifying the Medications and Cosmetics Act to increase from life imprisonment to death the maximum penalty for the sale and manufacture

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of counterfeit drugs causing significant damage or death. Increase penalties for comparable offences.[12]

Whistleblower Scheme

Since spurious or counterfeit pharmaceuticals affect the health of individuals and respect the country's pharmaceutical trade interests, it's urgent to tackle the problem. To eradicate the threat, the Central Government has altered a system to compensate whistleblowers who risk revealing criminals' identities.The Central Drugs Standard Control Organization's employees and informants are both eligible for this award programme (CDSCO).[14]

The following are the key components of the above-mentioned reward programme:

Figure 2 Key Components of the Whistle Blower Scheme[15]

Anti-Counterfeit Technology/Applications (WHO & IMPACT, 2008)

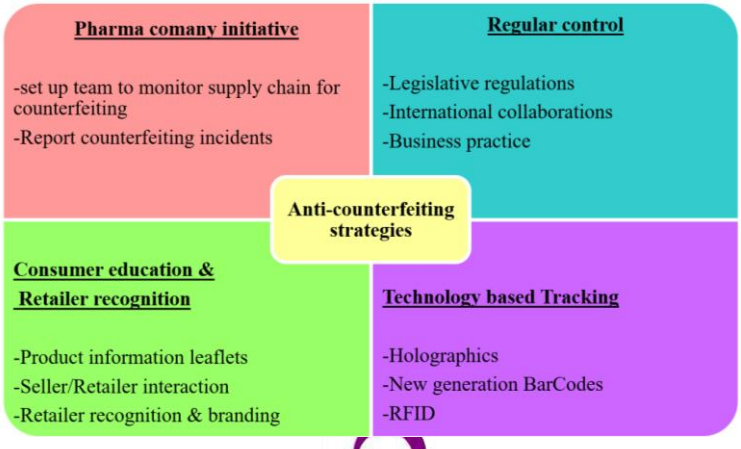
The reward programme must be used by informants in the pharmaceutical, cosmetic, and medical device industries	Informants can report drug manufacture, distribution, or adulteration to zonal and sub-zonal CDSCO personnel. Committee won't know whistleblower's identity	Whistleblowers are paid after CDSCO agents gather counterfeit, contaminated, and misbranded pharmaceuticals, cosmetics, and medical gadgets
The reward for the informant or officials will be up to 20% of the seized shipments' value, but never more than Rs 25 Lakh.	The award for a government or CDSCO officer shall never exceed Rs 5 lakh per case and Rs 30 lakh for their whole service	The informants will receive 25% of the total amount when the charge sheet is presented in court to avoid having to wait.

Implementing anti-counterfeit technologies is a key measure.[16]

The following categories can be used to categorise anti-counterfeit technologies:

a) Visible qualities include holograms, OVD, colour-shifting security inks and films, security graphics, sequential product numbering, and on-product marking.
b) Odours, substrates, embedded images, invisible printing, hidden marks, and digital watermarks are covert identifiers.
c) forensic methods such as DNA, isotope, and micro-tagging, as well as chemical and biological methods
d) Normalization and track & trace.[8][17]

Figure 3. Four-fold approach to fight the fake drug industry (adapted from Frost & Sullivan, 2008)



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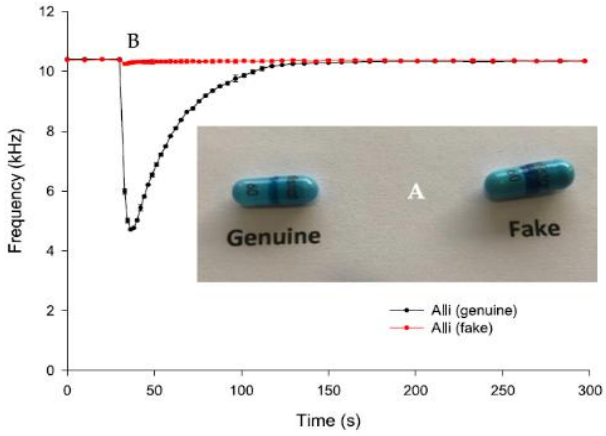
Broadband Acoustic ResonanceDissolution Spectroscopy (BARDS)

An audio spectrum is provided by the straightforward dissolution-based test known as BARDS. You may track and assess the breakdown of tablets and blends based on their acoustic spectrum after being dissolved in a solvent.[18]. Much work has gone into enhancing packaging security features or incorporating tracer elements in coatings[18]. However, a tablet's breakdown process has a distinct acoustic characteristic that serves as a strong product signature that counterfeiters are unable to duplicate just yet.[19]

Figure 4. (**A**) A picture of real and fake orlistat capsules. **(B)** 120 mg of real and fake orlistat powder were dissolved in 25 ml of water, according to BARDS data.



As shown in Fig. 3B, BARDS data clearly distinguishes between original and counterfeit orlistat. The actual capsule content caused a considerable decrease in the vessel's resonance frequency (fmin = 4.7 kHz). At 129 seconds, it reached a steady state once more, generating a V-shaped spectrum. The V-shape represents a rapid evolution of gas, followed by a slower loss of gas until equilibrium is reached. Falsified capsule content, on the other hand, does not affect frequency because there are no gas bubbles to evolve.[19]

Technology for tracking SSFFC/NSQ drugs

Decoding and simplifying the counterfeit pharmaceutical supply chain involves several different stepsAll pharmaceutical companies throughout the world likely utilise the product-based tracking system, which uses cutting-edge instruments to discover fraudulent pharmaceuticals on the market (Frost & Sullivan, 2008)[8]. These technologies include bar codes, holograms, and RFID (Radio-Frequency Identification)[20]. All of them have benefits and drawbacks, with RFID systems now considered the best while being the priciest. The disadvantages of this tracking technologyarethe same as the benefits.[8][20]

Figure 5. Drawbacks of Current technologies used for tracking counterfeit medicines

Measure	No success
Tamper evident packages	Not a problem for counterfeit, until it is multi-layered
Holographic and colour shifting effects	Expensive method- works only at packaging level
New generation bar code	Need a bar code reader cost over 2500
Radio Frequency Identification(RFID)	It is expensive. Moreover it is easy to clone an RFID tag by copying the contents of their memory and applying them to a new counterfeit tag which can then be attached to a counterfeit product

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CONCLUSION

False medications are a global problem, not just in India. Regulators, NGOs, and social organisations must work together to fight this problem. All organisations should spread information about fake pharmaceuticals to the public. Only law and order can eliminate the country's counterfeit drug problem. This review covers digital ways to combat fake medicine. This review examines the technology and techniques used in digital solutions and concepts to prevent fake and counterfeit pharmaceuticals. It also details the regions targeted to limit the use of counterfeit and fraudulent medicines.

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Conflict of interests

Authors declare no conflict of interest amongst themselves.

Ethical approval

Since this work does not involve any animal studies it does not require Ethical approval.

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