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Legal Perspective

Ethical and Legal Reflections on First-in-Class Drugs Exploring Biomaterials and Compulsory Licensing

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Access to life-saving medications for advanced stages of chronic diseases remains limited due to issues of affordability, availability, and accessibility. First-in-class (FIC) drugs, often central to treatment in such conditions, present a unique set of ethical and policy challenges. This study investigates the ethical dilemmas surrounding FIC drugs, including (1) high costs associated with new FICs, (2) limited accessibility, (3) monopolistic practices impacting equity, (4) tension between commercial interests and states obligations to uphold the right to health, and (5) increasing concerns regarding their availability. Using a medico-legal research framework, this study systematically explores how compulsory licensing (CL) could serve as a policy tool to address these dilemmas. A detailed literature review of the discovery, development, and regulatory approval of FICs, drawing from sources such as PubMed and the U.S. FDA was conducted. FICs are then categorized into two groups: (1) First generation FICs and (2) Second generation FICs, which are typically tested in targeted populations with well-defined phenotypes and genotypes, mimicked on *in vitro* systems exploring advanced biomaterial based technologies often allowing for faster and less costly approvals. However, the absence of a regulatory or ethical distinction between these two types has contributed to persistent inequities. A case analysis of India's first CL issued for sorafenib illustrates how policy responses can be shaped by real-world therapeutic effectiveness and alternatives such as lenvatinib. The findings support the argument that a nuanced classification of FICs, alongside experience-based compulsory licensing policies, may enhance the ethical distribution and health parity of innovative medicines. The study concludes that CL remains a vital mechanism for promoting the right to health, but its effectiveness depends on national policy contexts and recognition of the diverse nature of FIC innovation.

Introduction

Since the COVID-19 pandemic, there has been a significant trend in advancing healthcare through innovation, particularly with the approval of novel therapies and First-in-Class (FIC) drugs [1]. However, a concerning gap has emerged due to the lack of effective treatments for advanced stages of chronic diseases, which has led to an increased health disparity [2-4].

The relationship between the right to health and innovation in therapeutics is dynamic, interlinked, and evolving more rapidly than ever before [5, 6]. A deeper understanding of the molecular pathways leading to chronic diseases, such as cancer, has expanded significantly in recent years [7]. Cancer remains one of the top global public health challenges, around 20 million new cancer cases and 9.7 million fatalities were reported worldwide in 2022 [8]. Cancer is a disease where certain body cells grow uncontrollably and spread to other parts of the body [9,10]. It is driven by genetic changes, with each individuals cancer having a unique combination of mutations [11]. Different types of cancer exhibit various manifestations, prognoses, and responses to treatment. Post-COVID, cancer mortality rates have risen and warrant urgent attention [12].

In clinical practice, there are cases where all approved treatments for a particular disease show insufficient effectiveness or where no effective medicines exist at all [13,14]. In such instances, the development of innovative new drugs, including FIC drugs, is essential. However, the cost of these new drugs, especially for treating cancer, is exorbitant and continues to rise [15]. This calls for a reduction in development timelines and acceleration of

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approval processes [16]. To address this, state agencies are adopting new strategies and designations to improve accessibility.

First-in-Class (FIC) drugs refer to new medications that have never been approved by regulatory authorities of the state before [17,18]. There has been a steady increase in FIC drug approvals in the post-COVID period. For instance, the FDA defines an FIC drug as a drug molecule (chemical or biological) that has never before been approved by the utilizing an entirely new therapeutic mechanism, this FDA-approved drug is designed to treat a specific health disorder [19, 20]. This category includes many breakthrough therapies, such as drug-antibody conjugates, advanced therapies, and orphan drugs. While FIC drugs do not have a separate regulatory status, their affordability and accessibility are significant concerns, as their prices are often prohibitively high. State-led strategies are necessary to reduce prices and improve access [21].

Innovation in drug development requires substantial investment from pharmaceutical and biotech companies [22-24]. FIC drugs often become blockbusters, generating significant revenue, which is crucial for sustaining ongoing innovation [25,26]. However, most of the investment in the early phase of a product's market introduction is made by inventors, making medicines expensive during this period [27]. This results in unequal distribution, exacerbating health disparities [28]. The state has an obligation to ensure the right to health for all citizens [29]. Compulsory licensing, as outlined in the Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement, addresses the global right to health and aims to ensure the equitable distribution of advanced medicines [30]. However, the accessibility of these medicines still depends significantly on the purchasing capacity of both the state and the patients [31,32].

This legal analyses aim to assess, (1) the process of FIC drug development, (2) the major factors affecting the distribution of FIC medicines, (3) impact of inventors rights on FIC medicine distribution, (4) the states obligation to ensure the equal distribution of medicines, (5) the role of compulsory licensing in ensuring the equitable distribution of FIC medicines. By addressing these points, this study seeks to propose a sustainable ecosystem for FIC medicines, focusing on the rationale for their use and the potential of compulsory licensing to alleviate health disparities

Materials and Methods

FIC Approval Process: The methodology involves an in-depth study of the process by which First-in-Class (FIC) drugs are discovered, developed, and approved by the FDA. This is done through a detailed literature review, including PubMed, FDA website, and other relevant online resources. The various stages of drug development are analyzed, with a particular focus on how these stages are utilized in the regulatory approval process. A detailed comparison is made between the approval process for FICs and other drugs, highlighting the unique considerations involved. Additionally, the incorporation of new scientific and technological developments into the regulatory approval process is explored. A major area of analysis is the significant difference in the target population and use of advanced biomaterial based technologies in the drug discovery process of first generation vs. second generation FICs.

Classification of FICs: A classification strategy is employed to differentiate FICs based on the time and expense required for approval. The classification is further refined by considering the target population of the first generation vs. second generation FIC drugs. This classification is used as a foundation for analyzing the ethical dilemmas surrounding FIC drug approval and accessibility. The criteria for classification are designed to provide insights into the ethical issues related to affordability and accessibility.

Analysis of Ethical Dilemmas Using the New FIC Classification: This newly developed classification strategy is applied to analyze several ethical dilemmas. The first ethical dilemma examined is the persistent low affordability of first vs. second generation FICs despite advances in science and technology. The classification strategy is applied to investigate why affordability and accessibility issue continues to be a challenge. The second ethical dilemma explored is the low accessibility of FICs. The impact of the classification strategy is analysed to understand the underlying reasons for this issue in detail. Additionally, the strategy is used to examine how monopolies in the pharmaceutical industry may contribute to reduced affordability and accessibility of medicines. Finally, the classification strategy is used to analyze how the state can prioritize efforts to ensure the right to health for all, considering the challenges of affordability and accessibility.

Analysis of Compulsory Licensing Policy: The methodology concludes with an analysis of how compulsory licensing can address these ethical dilemmas and its potential effects on the accessibility and affordability of FIC drugs. A case study is conducted to highlight the need for developing a compulsory licensing policy based on the experiences of states that have implemented such policies. The case study provides practical recommendations for overcoming barriers related to drug access and affordability through the use of compulsory licensing.

Results and Discussion

Ethical dilemmas of first generation Vs. second generation first-in-class (FIC) drugs for advanced stages of chronic diseases

The FIC discovery, development, and approval process

To understand the significant expenses involved in the development of FIC drugs, it is essential to examine the complexity of the drug discovery process. FIC drugs are often designed for specific patient populations whose conditions cannot be treated by conventional medicines. For example, in oncology, there are notable cases such as Inotuzumab ozogamicin, an Anti-CD22 monoclonal antibody-drug conjugate approved for relapsed or refractory B-cell precursor acute lymphoblastic leukemia in 2017, and Tagraxofusp, a fusion protein targeting plasmacytoid dendritic cells for blastic plasmacytoid dendritic cell neoplasm. Another example is Midostaurin, a multi-target tyrosine kinase inhibitor for acute myeloid leukemia. These drugs target specific populations that require specialized treatment, often combining expertise from multiple disciplines such as drug discovery, drug delivery, and biotechnology.

The approval of such drugs follows the regular regulatory pathways, which require the demonstration of safety and efficacy. The ethical dilemma here revolves around whether a new approach to drug discovery could reduce the time and cost of development for these FICs, making them more affordable and accessible. To address this, the medico-legal foundations of the drug discovery and development process need to be analyzed in detail.

The drug discovery process generally involves five main stages as per conventional (medico-legally accepted) procedures, (I) pre-discovery stage; basic research is conducted to understand the mechanisms of diseases and propose possible targets. (ii) drug discovery stage, where scientists look for molecules or therapeutic

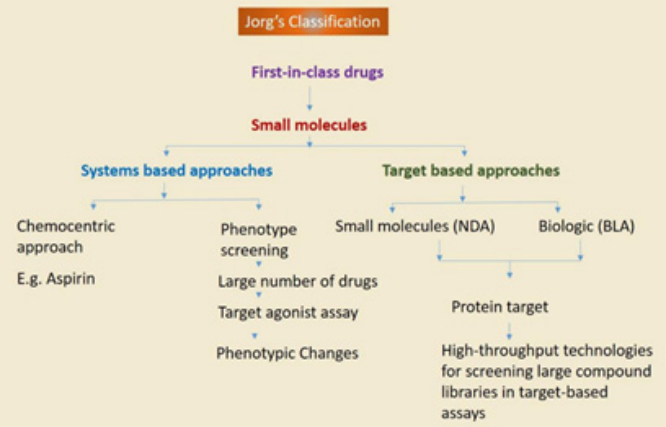


Figure 1: Jorg's classification of FIC drugs

plans that can treat the disease or alleviate symptoms. (iii) preclinical development stage, this focuses on clarifying the mode of action of drug candidates, investigating toxicity, validating efficacy in vitro and in vivo, and evaluating formulations. (iv) clinical stage, here the drug candidate is tested in humans through clinical trials. And finally the (v) review, approval, and post-market monitoring stage, where evaluates whether the drug should be approved based on clinical trial results [33]. These stages, while commonly referred to as pre-discovery, preclinical, and clinical stages in the literature, typically span many years (5-6 years for pre-discovery and 2-3 years for preclinical testing). Toxicity studies are conducted in both rodent and non-rodent models before the drug advances to human clinical trials. As illustrated in figure 1, Jorg's classification of FIC drugs [34] identifies a well-defined target population with distinct phenotypic and genotypic characteristics.

The clinical trial process begins once an FIC drug is approved as an Investigational New Drug (IND) [35]. The trials are conducted in phases, such as (1) Phase 0: Optional, first-in-human trials that assess pharmacokinetics and pharmacodynamics using low, nontherapeutic doses in a small group of participants [36]. (2) Phase 1: Safety trials that help determine the safe dose range and identify side effects, typically conducted on 20 to 60 healthy volunteers [37]. (3) Phase 2: Expands the testing to a larger group to evaluate the drug's efficacy and further assess safety. (4) Phase 3: Multicenter trials with up to 3,000 participants, focusing on confirming the drug's safety, efficacy, and benefits. (5) Phase 4: Post-market trials to monitor long-term safety and efficacy after the drug is approved.

The traditional drug development process is lengthy and costly, often leading to high prices for FIC drugs. This raises an ethical dilemma: why can't a new, more efficient route for drug discovery be adopted for FIC drugs that would reduce development costs and time, ultimately ensuring affordability and accessibility?

The process of drug discovery and development is legally structured and follows a gatekeeping approach to maximize benefits while minimizing risks. However, emerging developments in advanced biomaterials, molecular biology, chemistry, biotechnology, and computational modeling suggest that faster drug screening and approval processes may be possible, particularly for FIC drugs with well-defined target populations. These advances could potentially streamline drug development by reducing the need for extensive preclinical and clinical studies, thereby cutting costs and time. Historically, the drug approval process was based on a broad, undefined patient population. However, with advancements in molecular biology, the phenotypic and genotypic characteristics of target populations are now well-defined. Advanced biomaterial based technologies help to mimic the different stages This shift allows for faster drug screening, potentially eliminating many preclinical and clinical stages. This reduction in time and cost presents an opportunity for regulatory agencies to adopt new pathways for approving FIC drugs, specifically those with defined target populations. Such pathways could expedite FIC approval, reduce costs, and improve affordability.

Given this, we propose classifying FICs into two categories, (1) First generation FICs, where drugs developed through traditional methods with undefined target populations. (2) Second generation FICs, here drugs developed with advancements in biomaterials, molecular biology and biotechnology, targeting well-defined phenotypic and genotypic populations. This classification can aid in identifying new approval pathways that reduce the time and cost of FIC drug development, addressing ethical concerns related to affordability and accessibility.

Why FICs are not affordable

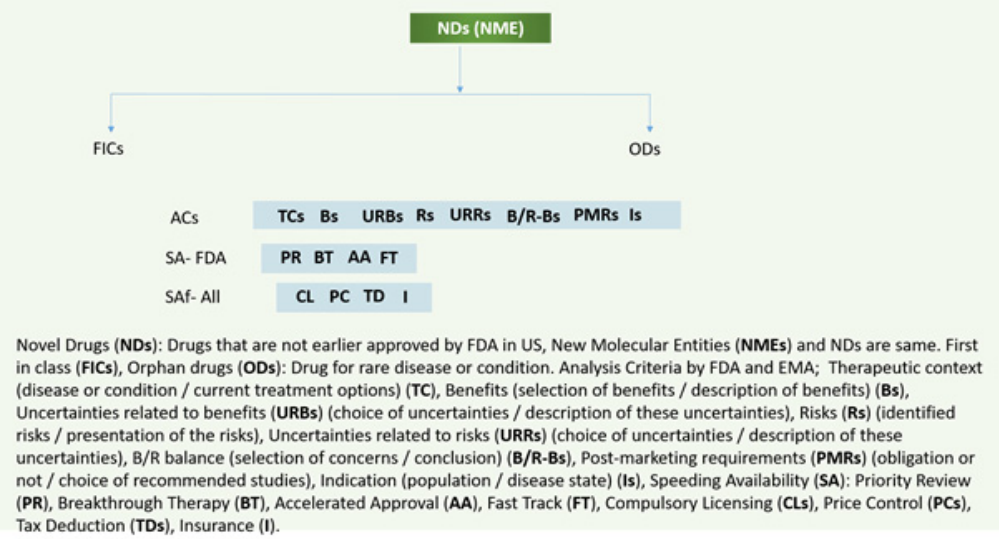
From the above analysis, it is evident that the discovery and development of First-in-Class (FIC) drugs involve a high degree of inventive steps and represent a highly risky investment. As a result, these drugs are typically protected by intellectual property (IP) rights and enjoy a period of market exclusivity, contributing to their high price. However, based on the innovation landscape, FICs can broadly be classified into two categories: (1) First generation FICs and (2) Second generation FICs as proposed here.

Second generation FICs are increasingly being approved at a faster rate due to advancements in biomaterial led drug screening, molecular targeting, and precision medicine. These innovations, leveraging genomics and proteomics, help streamline drug discovery and reduce the time and cost required to bring medicines to market. Unlike conventional first generation FICs, the second generation FICs target a genetically and phenotypically well-defined population, which can be identified using advanced biomaterial based screening systems and molecular diagnostic tests. Clinical trials for these populations are often more focused, involve smaller sample sizes, and demonstrate clear clinical benefits mimicked in *in vitro* systems more rapidly. Therefore, regulatory agencies should recognize this classification and adopt differential regulatory and pricing approaches, especially for second generation FICs. Scrutinizing second generation FICs based on the reduced complexity of their development can help lower their cost and improve affordability, distinguishing them from traditional large-scale, population-based first generation FIC development models.

Why is accessibility of FICs low and how can it be improved?

A key ethical dilemma in global health is the limited accessibility of FICs, particularly in low- and middle-income countries. Although FIC drugs often become blockbuster therapies due to their innovation and therapeutic impact, the high cost set by pharmaceutical companies restricts their accessibility, especially among poorer populations in underdeveloped nations [38].

Globally, nearly two billion people lack access to essential medicines, and over ten million deaths occur annually due to the unavailability of advanced treatments [39]. A primary factor contributing to this inaccessibility is the high cost of drugs, which stems from various elements throughout the R&D pipeline. Drug development involves extensive preclinical research, target identification, and the establishment of mechanisms of action, processes that can span



Novel Drugs (**NDs**): Drugs that are not earlier approved by FDA in US, New Molecular Entities (**NMEs**) and NDs are same. First in class (**FICs**), Orphan drugs (**ODs**): Drug for rare disease or condition. Analysis Criteria by FDA and EMA; Therapeutic context (disease or condition / current treatment options) (**TC**), Benefits (selection of benefits / description of benefits) (**Bs**), Uncertainties related to benefits (**URBs**) (choice of uncertainties / description of these uncertainties), Risks (**Rs**) (identified risks / presentation of the risks), Uncertainties related to risks (**URRs**) (choice of uncertainties / description of these uncertainties), B/R balance (selection of concerns / conclusion) (**B/R-Bs**), Post-marketing requirements (**PMRs**) (obligation or not / choice of recommended studies), Indication (population / disease state) (**Is**), Speeding Availability (**SA**): Priority Review (**PR**), Breakthrough Therapy (**BT**), Accelerated Approval (**AA**), Fast Track (**FT**), Compulsory Licensing (**CLs**), Price Control (**PCs**), Tax Deduction (**TDs**), Insurance (**I**).

Figure 2: Shows the management of approval process of FICs by regulatory agencies mainly by US-FDA to ensure the medicines to their respective population and world in general

many years and cost millions of dollars [40]. Additionally, the complexity and scale of clinical trials, which often require large patient cohorts and prolonged follow-up add significantly to the financial burden. It is estimated that the cost of developing a new drug ranges from $314 million to $2.8 billion (Ocran Mattila et al., 2021; Vincent Rajkumar, 2020), and the entire process typically takes around 12 years.

However, this generalization may not fully reflect the evolving landscape of second generation FIC development. As discussed earlier, many new FICs are developed for highly specific, well-characterized patient groups. With precise molecular diagnostics and targeted designs, these drugs can undergo streamlined approval processes. Therefore, if regulatory bodies and policymakers recognize this distinction and adjust approval protocols and pricing models accordingly, the affordability - and thus accessibility - of second generation FICs can be significantly improved.

Monopoly reduces affordability and accessibility of FICs

Another persistent ethical concern is the role of market monopoly in escalating the cost of FICs. Patent protection allows pharmaceutical companies to set and maintain high prices, restricting access for a significant portion of the global population - particularly in low-income countries. In the context of diseases like cancer, where many FICs are indicated, the unaffordable cost of innovative therapies contributes to increased disease severity and mortality.

Sustained monopolistic pricing of such medicines imposes a heavy financial burden not only on patients but also on families and national healthcare systems. Governments worldwide have a fundamental obligation to ensure equitable access to healthcare as a basic human right. This includes the availability and affordability of essential medicines necessary to meet a population's core health needs.

While IP protections are vital for incentivizing innovation, current frameworks often fail to consider the reduced novelty or complexity of some recent FICs, here considered as second generation FICs, particularly those developed through high-throughput screening and molecular targeting of well-characterized populations using advanced biomaterial based technologies. These modern drug discoveries, while still valuable, may not involve the same level of innovation as historical breakthroughs. Therefore, it is both ethical and practical to reconsider IP laws, potentially linking patent scope and duration to the degree of inventive steps involved. Such a revision could enable a more balanced system—encouraging innovation while also allowing earlier entry of generics or follow-on innovations. Wherein, second generation FICs can be considered as follow-on solutions. This approach would help reduce drug prices and significantly improve access to FICs, especially in resource-limited settings.

State's obligation to ensure the affordability of medicines is being compromised

Another major ethical dilemma is the perceived inaction of the state in balancing the inventor's commercial interests with the public's right to health. A significant factor impeding the realization of the right to health is the patent protection granted to FICs. Patents can adversely impact accessibility, primarily through the unaffordability of new FIC medicines.

Pharmaceutical companies, having invested substantial time, money, and infrastructure in drug development, particularly for major diseases like cancer often anticipate profit maximization through strategic patenting strategies (Denault and Tramoy, 2024). Once granted, patents empower these companies to set high prices for their products. Ever greening is another controversial strategy adopted by pharmaceutical companies to extend their monopoly beyond the original patent expiry. This involves filing for secondary patents based on slight modifications or new uses of the existing compound. These follow-up patents, which are often easier to secure, serve as part of lifecycle management, further delaying the entry of generic alternatives [41, 42].The combination of robust primary and secondary patents creates a strong market exclusivity shield, restricting competition and prolonging high prices. Consequently, FIC approvals often become another tool to ensure continuous innovation pipelines, rather than serving immediate public health interests. In response to this, agencies like the US

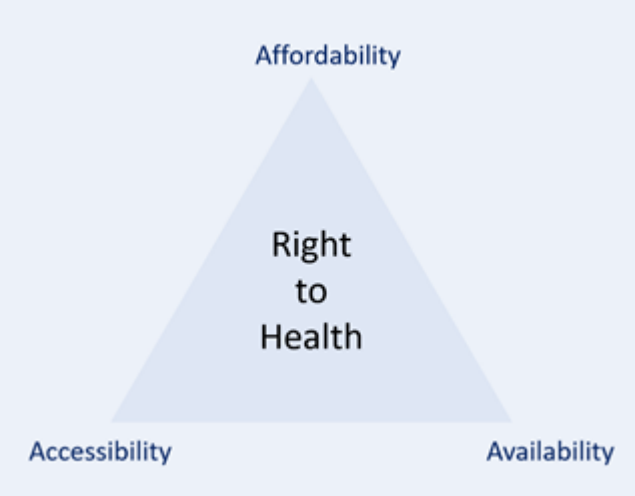


Figure 3: Three critical challenges affecting equal distribution of medicine to all and thus right to health

FDA have introduced expedited approval mechanisms to fast-track the availability of innovative drugs (see figure 2). Many other regulatory bodies worldwide follow similar frameworks aimed at reducing time-to-market for promising therapies.

While faster approvals have advantages such as encouraging innovation and creating long-term competition these expedited frameworks have yet to fully integrate genotype- and phenotype-based drug screening, which is the cornerstone of personalized medicine. Adopting such approaches could significantly enhance the value and cost-effectiveness of FICs in the near future.

Beyond affordability and accessibility: The availability crisis of FICs

An emerging ethical concern is the limited availability of FICs, especially for patients in advanced stages of chronic diseases. This presents a critical challenge to the principle of equal healthcare distribution, which is central to the right to health. Access to medicines should not be determined by socioeconomic status, and the state bears the responsibility to ensure equitable distribution.

The interrelation between affordability, accessibility, and availability of medicines forms the foundation of equitable healthcare (see figure 3).

Despite being available in the market, patented FICs are often unaffordable to large segments of the population. Conversely, non-patented drugs, though generally more affordable and accessible, are often exported in large volumes, reducing their availability in local markets particularly in low- and middle-income countries.

The figure 4 illustrates the paradox: patented drugs suffer from limited affordability and accessibility, while generic drugs face availability constraints due to export-oriented marketing strategies. Both scenarios hinder equitable access. To address this, legal and trade provisions must be re-evaluated. Policies should be designed to prioritize local healthcare needs over international market capitalization. This includes enforcing local manufacturing quotas, export limits during shortages, and price regulation mechanisms to ensure that both patented and generic drugs are accessible, affordable, and available for all.

Role of Compulsory Licensing in Ensuring the Availability Factor Beyond Affordability and Accessibility, Without Undermining Innovation

Compulsory licensing has emerged as a powerful legal tool to address the availability of essential medicines often overshadowed by the focus on affordability and accessibility. Availability, a critical dimension of the right to health, refers to ensuring that medicines are physically present in sufficient quantities for all those who need them. It is one of the most pressing challenges faced by governments globally, especially in the context of high-cost patented drugs such as FIC molecules. As Stavropoulou and Valletti have noted, availability is predominantly a state responsibility and can be complex to enforce effectively [43].

Pharmaceutical patents, although vital for incentivizing innovation, frequently impede availability by giving exclusive manufacturing and distribution rights to patent holders. This often leads to monopolistic pricing strategies and a lack of widespread distribution, particularly in low- and middle-income countries (LMICs). Governments must therefore play a more interventionist role to ensure these life-saving innovations reach all segments of the population [44].

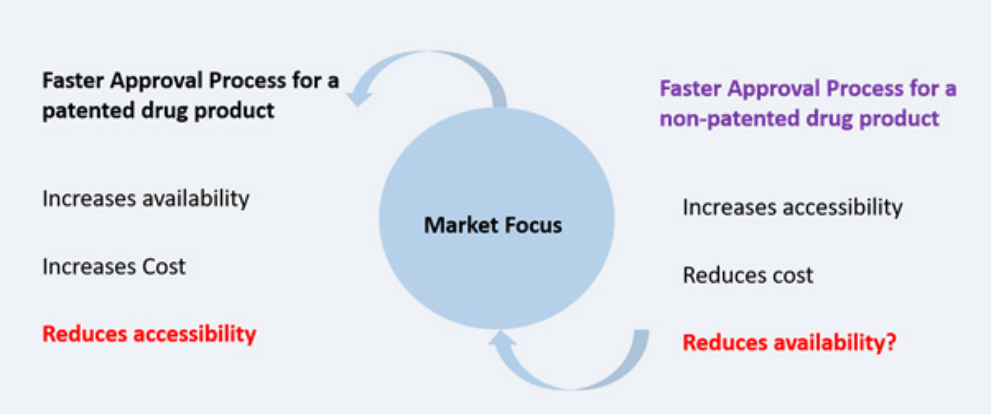


Figure 4: Dynamic market behaviour of patented and non-patented drug products affecting equal distribution of drugs

To balance intellectual property rights with public health, the World Trade Organization (WTO) introduced the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement in 1995. The Doha Declaration of 2001 further emphasized the flexibilities within TRIPS, especially for public health emergencies, permitting the issuance of compulsory licenses [45].

A compulsory license is a non-voluntary authorization granted by a government to a third party, allowing them to produce and sell a patented product without the patent holder's consent, subject to specific conditions (Vawda, 2022). Article 31 of the TRIPS Agreement outlines this mechanism, including the requirement for prior negotiation with the patent holder except in circumstances of national emergency, public non-commercial use, or anti-competitive practices. This framework enables governments to circumvent the barriers posed by patent monopolies, particularly when the price, production capacity, or intent of the patent holder restricts access. The Doha Declaration marked a paradigm shift by recognizing the right of member states to protect public health and promote access to medicines for all.

Importantly, compulsory licensing does not negate innovation; instead, it offers a check against misuse of patent rights. By imposing obligations on patent holders to supply drugs at fair prices and in adequate quantities, it reinforces the principle that patents should serve public interest in addition to private profits. This is particularly relevant for FIC drugs, which may otherwise remain inaccessible due to their novelty, exclusivity, and high development costs.

Furthermore, expanded grounds for issuing compulsory licenses include:

- Failure to locally manufacture or adequately supply the patented medicine.
- Harm to public interest by the patent holder or licensee.
- Exorbitant pricing not aligned with production costs.
- Risk of interrupted supply of essential drugs.
- Need to enhance local manufacturing and technology transfer.
- Evidence of anti-competitive behavior.
- Public health emergencies.
- Import/export scenarios where a country lacks manufacturing capacity.

The dual licensing framework allows a country to issue a license to import patented medicines and another country to issue a license for export, thus enabling global cooperation in public health efforts. This is particularly vital for LMICs with limited manufacturing infrastructure. Overall, compulsory licensing enhances the availability of new FIC medicines without undermining innovation. Instead, it promotes responsible innovation, where market exclusivity is conditional upon ensuring social benefit. The state thus has a constitutional and ethical obligation to use such tools judiciously to fulfil the right to health.

Remuneration of the patent holder for sustainable invention

Article 31(h) provides adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization. The remuneration has to be decided by the authorities in the country concerned. Any decision relating to the remuneration shall be subject to judicial review or other independent review by a distinct higher authority.

The figure 5 shows the comparison between India and US policies

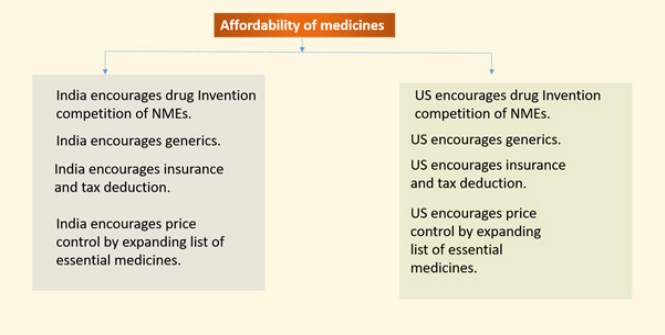


Figure 5: Affordability of medicines: Ensuring innovation and distribution of medicines a comparison between the Indian and the US strategies

influencing the FICs reaching market and which is going parallel to each other. However, approval of FICs differ between developed (US) and developing (India) nations. This is mainly because the developing nations don't invest in research and innovations like developed countries.

Overall, the low FIC innovation and availability of medicines significantly affect the Right to Health in developing countries like India.

The figure 6 shows how compulsory licensing vs. voluntary licensing is promoting drug invention competition while ensuring the drugs to all. From figure 6, shows compulsory licensing improves affordability, accessibility, availability and innovation while voluntary licensing improves the first three and it suppresses innovation. From this discussion about compulsory licensing it is apparent that it is a superior tool for states to make available the FICs to treat advanced stages of chronic diseases.

Case Study: Sorafenib Tosylate and the Role of Compulsory Licensing in Reducing Health Disparities

In 2012, India issued its first-ever compulsory license (CL) for the anticancer drug Sorafenib Tosylate (ST), granting Natco Pharma the right to manufacture and sell the drug at a significantly lower price. At the time, Bayer held the patent and monopoly rights for ST, which was primarily used to treat renal and hepatic cancers. The compulsory license mandated a 6% royalty payment to Bayer, a move supported by public health advocates to enhance drug affordability and accessibility in India [46].

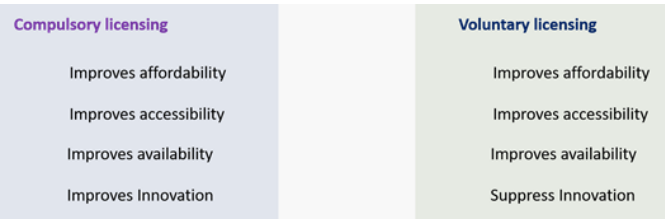


Figure 6: Comparison between compulsory licensing and voluntary licensing in FIC innovation and market dynamics

Following the issuance of the CL, the government slashed the price of Sorafenib by 97%, reducing the cost for 120 tablets from approximately 2.86 lakh to 8,880 [47]. With nearly one lakh people in India affected by renal and hepatic cancers annually and a 30% rise in new diagnoses coupled with a 24% mortality rate this policy intervention aimed to alleviate the burden of cancer-related deaths by making treatment more affordable.

However, despite increased affordability, significant improvements in survival outcomes were not observed. Clinical studies from India reported a median progression-free survival (PFS) of just 4.2 months for Sorafenib, with higher toxicity and discontinuation rates compared to Western studies [48]. This discrepancy may be attributed to factors such as, (i) Pharmacogenomic differences: Dosing regimens effective in Western populations may not be optimal for Indian patients. (ii) Adherence-related issues: High toxicity led to discontinuation, which we define here as a lack of "adherability", the patient's ability to continue therapy effectively. Lenvatinib, a newer agent, demonstrated superior therapeutic outcomes. In global trials, it nearly doubled the progression-free survival compared to Sorafenib [49]. Indian studies mirrored these positive outcomes [50], indicating that Lenvatinib is both clinically effective and better tolerated.

Despite this, Lenvatinib remains costly in India, and no compulsory license has been granted for its production. This highlights a gap in policy, where the selection of drugs for compulsory licensing should be more strategic and based on both clinical efficacy and population health impact. The Sorafenib CL improved affordability, accessibility, and availability, but failed to address adherability a crucial determinant of therapeutic success. In contrast, Lenvatinib exhibits high actionability (defined here as the likelihood of translating clinical efficacy into real-world outcomes), yet remains financially inaccessible for many patients.

This calls for a well-defined compulsory licensing policy that prioritizes:

- Evidence-based selection of candidate drugs, here onwards it can be considered under first generation FICs and second generation FICs.
- Evaluation of clinical actionability and adherability,
- Integration of pharmacogenomics and real-world tolerability data.

Furthermore, there is an urgent need to foster innovation and local research to enhance the acceptability of treatment modes, and to support the development of novel, affordable FIC therapeutics.

Conclusion

This study critically examines the development and deployment of first-in-class (FIC) therapeutics in the context of unmet clinical needs, particularly in chronic diseases such as cancer. The analysis highlights two distinct categories of FICs: (1) First generation FICs developed by targeting broader patient populations and (2) Second generation FICs designed for narrowly defined, often genotypically or phenotypically stratified cohorts, mimicked in advanced biomaterial based screening systems. The latter offers the advantage of reduced development timelines and costs in second generation FICs, but also requires refined regulatory considerations that balance innovation incentives with patient access.

The case study of Sorafenib Tosylate underscores the limitations of compulsory licensing (CL) when applied without robust clinical and pharmacoeconomic evaluation. While the CL significantly improved affordability and access, it did not translate into better patient outcomes, largely due to issues related to toxicity, dose appropriateness for the Indian population, and poor adherence, collectively referred to as "adherability." In contrast, Lenvatinib, although not covered by CL, demonstrated superior clinical outcomes and better tolerability, indicating higher "actionability" in the Indian setting.

These findings emphasize the need for a comprehensive, evidence-based compulsory licensing policy that considers not only the legal and economic dimensions but also integrates real-world clinical data, pharmacogenomic relevance, biomaterial based screening strategies, treatment adherence, and population-level effectiveness. Additionally, enhancing domestic research capacity and promoting innovation are critical for improving the acceptability of new treatment modalities and ensuring equitable healthcare access.

A refined CL framework anchored in real-world data and public health priorities could serve as an essential tool in addressing drug affordability and bridging therapeutic gaps in low and middle-income countries. Future policy efforts should focus on aligning regulatory pathways, intellectual property strategies, and healthcare delivery models to support sustainable innovation while ensuring equitable access to life-saving medicines.

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