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Commentary

"Drug Repurposing" Policies and Statutes: Lessons from the COVID-19 Pandemic:A Review

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ABSTRACT

Introduction: Repurposed drugs are not eligible for patent protection in India vide Sec 3 (d) of the Indian Patent Act, 1970. The data generated to establish the therapeutic efficacy of the repurposed drugs for the new indication are not eligible for data exclusivity under the provisions of the Drugs and Cosmetic Act, 1940. However, repurposed drugs possess immense advantages, especially when compared to the traditional route of drug discovery. Marketing repurposed drugs is fraught with challenges, and means to overcome them need to be facilitated. **Methodology:** A review of literature regarding provisions available to protect repurposed candidates through various routes globally were studied including policies, special committee reports as well as case laws. **Results:** A brief tenure of data exclusivity for repurposed candidates as provided in statutes in the US and EU appears to be an attractive route of protection of such inventions. This will encourage and incentivize drug research by this route and eventually lead to a fulfillment of India being a preferred destination for not only pharma manufacturing, but also research.

Keywords: Repurposing drugs, Patents, Data exclusivity, COVID-19, Drug discovery, Drug development in India.

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INTRODUCTION

New drug discovery is a highly risk prone, resource intensive process in terms of capital investment and time. The process of discovering a new drug costs up to 1.4 billion $ over a time frame of 12-15 years.[1,2] The process begins with the identification of a target, followed by arriving at a chemical or biological scaffold that will act on the target, synthesizing the drug candidates, developing assays to study the efficacy of the drug candidates, testing them *in vitro* for efficacy, profiling their safety in animal models, experimenting and optimizing to achieve desirable and druggable properties, formulating a stable dosage form and concluding by conducting phased clinical trials in humans.[2] The data generated through these various stages is submitted to regulatory authorities for seeking marketing approval. The process usually has a very high attrition rate, that is, from tens of thousands of new molecules which may potentially possesses activity against a target, it is only one new molecule that ultimately complies with all the criteria to be eventually approved for marketing. One of the main reasons for the high rate of failure of molecules in the process of drug discovery is poor safety profile, leading to their elimination from the process.[3] These failures contribute substantially to the cost of drug discovery. After obtaining marketing approval from the regulatory authorities, the pharmaceutical innovator organization furthers the process of drug discovery by continuing research on the new molecule leading to several innovations (e.g.: improved processes, new forms with enhanced performance related properties and proposing a second medical use). The objective of such pursuits is to create a portfolio of intellectual property rights that can aid in retaining and if possible extending the monopolistic rights derived from them.

The quantum of resources invested in the process of drug discovery is earned back by the innovator when they obtain the monopolistic rights that patents provide for the new entity. The innovator usually ploughs such earnings back into the process of drug discovery. Thus, patent protection is a very critical and an integral part of the new drug discovery programme of an innovator organization. The need for a strong patent protection is so much desired that some molecules may not be actively considered by the innovator in a drug discovery programme if their patent prospects are poor.[4]

The myth of "one drug, one target" was exploded by quoting several examples and studies.[5] Eflornithine, Pentamidine, Celecoxib, Tamoxifen, Sulindac, Astemizole and Closantel are some of the drugs described for new uses. The authors further stated that 62% of the drugs listed in PubChem bind to more than one target. They opined that the promiscuous binding of drugs

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caused adverse effects, but simultaneously opened the gates for their repositioning.[5]

Drug repositioning is the process of identifying a new indication for a drug or a drug candidate outside the scope of the original indication.[3] Repositioning is also termed as repurposing, drug reprofiling, reused medicament, therapeutic switching, second medical use or second indication.

In a process of repurposing, a safe drug candidate that has been approved for marketing or is eligible for a marketing approval is evaluated for a possible second medical use. This provides two significant beneficial features: no attrition in pre-clinical stage and substantially decreased risk factors in the process. Thus, with a safe candidate identified, the cost of drug discovery process is limited to the evaluation of its activity, making the process less time consuming and economical up to even 60%.[5]

Repurposing as an alternate route to drug discovery is highly evident in these current pandemic times. Established drugs such as Remdesivir, Falcipiravir and Tocilizumab were granted emergency use approvals against the SARS-CoV-2 virus. Many more drugs such as Hydroxy Chloroquine, Ivermectin, Doxycycline, Ritonavir and Lopinavir were explored to treat the infected patients.

Issues and Challenges in Repurposing Drugs

Protection through patents and drug regulations

New drug molecules are eligible for patent protection for 20 years from the date of filing of a patent in accordance with the Agreement on Trade Related Intellectual Property Rights (TRIPs).[6] On the other hand, the second medical use or new use or new property of a known substance is not patentable in several countries including India and Indonesia to name a few.[7,8] Europe provides patent protection to a second medical use through Swiss claims which reads as "Use of substance X for the production of a medicament to treat disease Y" and the US patent act allows "A method of treating condition X with medicament Y".[9] But the latter construct of claims is also not allowed in many European, Asian and South American countries.[10] A point to be noted at this juncture is that these exclusions are in accordance with the provisions in the TRIPs agreement.

One more route of protection that is available for repurposed drugs in Europe and US is for the data generated during the conduct of clinical trials to be submitted to regulatory authorities. This form of protection termed as "data exclusivity" translates into a certain period within which a generic manufacturer cannot refer to the data generated by the innovator to seek marketing approval. The US provides data exclusivity of five years for a new chemical entity and three years for a second indication and EU drug laws provide data exclusivity for eight years for a new chemical entity and an additional year if the second indication is discovered within those eight years.[11,12] The Drugs and Cosmetics Act implemented in India states that a new drug will remain so for a period of four years, implicating that if a generic seeks to enter the market within four years of the entry of a new drug, then they will need to submit clinical data as required for a new drug, to be granted a marketing approval. Thus, while India does not explicitly offer a regime for protection of data, however, the fact that generic companies will not be in a position to conduct trials to seek approval and would rather wait for four years for the drug to be declared as not new indirectly provides the new drug with data exclusivity. Further, there is no such provision for the repurposed drugs in India.[13]

Thus, in conclusion it may be stated that in spite of the cost and time benefits and the possibility of repositioning a number of drugs, the route of repurposing is not so popular. The pharmaceutical organizations have no globally harmonized, uniform avenue available to protect their invention and recover the amount invested in clinical trials. Moreover, the system does not facilitate a method of detection of infringement for medicaments approved for their second medical use. A case in point is elaborated herein.

Infringement of patentee`s rights

The issue of distinguishing the repurposed product from that of the innovator`s product, generics or branded generics in the market is very challenging and acute. Repositioned products are marketed with a skinny label, wherein the indication is carved out of the innovator`s label. The skinny label describes the intended new use and marketing approval is only for this new indication. However, infringement of patentee`s rights due to erroneous prescribing or dispensing is difficult to detect, as evidenced in the case law on pregabalin in UK.[14]

In end 2018, the UK Supreme court decided on the pregabalin case, where the claim in contention was the second medical use of a drug for pain. The patent rights for pregabalin as a drug marketed under the name Lyrica rested with the Pfizer group company, Warner Lambert and expired in 2013. Then Warner Lambert proposed and obtained patent rights for using pregabalin for relief of various types of pain such as neuropathic pain, inflammatory pain and idiopathic pain as a second medical use of pregabalin. The primary use of pregabalin was for the treatment of epilepsy and general anxiety disorder (GAD).

Actavis began marketing pregabalin as a generic with a skinny label for treatment of epilepsy and for GAD (and not indicated for pain) under the brand name Lecaent, which translates into the fact that Actavis was marketing Lecaent for patent expired indications. With the introduction of Lecaent, Pfizer started observing a loss in market share, especially in UK, where prescriptions are written with only the generic name of the drug. Pfizer tried to make the Physicians realize that the prescription of Actavis` Lecaent for neuropathic pain was amounting to infringement of their patent rights. But Pfizer did this through the issuance of letters to

Physicians allegedly containing "threatening" language. However, this eventually proved to be counterproductive.

Warner approached the Courts to stop the infringement of the second use patent, since they observed an almost 50% effect on their market share on the entry of the cheaper generic, Lecaent. Physicians in UK prescribe drugs using their International Non-proprietary Name (INN), the pharmacists do not know the indication for which the prescription is written and hence are obliged to sell the cheapest drug, which is the generic, in this case Lecaent. Thus, Lecaent was being sold for the treatment of pain too.

After a series of legal proceedings, the matter reached the UK Supreme Court (UKSC),[14] and in November 2018 the UKSC opined on matters relating to infringement of second use patents-by manufacturer, physicians, pharmacists and patient and further on the validity of claims in the second use pregabalin patent of Warner, EP 0934061.[15] The Court upheld only the claims of the Warner patent for relief of inflammatory pain, while the claims related to neuropathic pain were considered invalid. The Court further held that even if the claims were all valid, there was no intent to infringe the claims by the manufacturer, since he is manufacturing and marketing with a skinny label for the treatment of epilepsy and GAD. The physicians, pharmacists and patients were not infringing the claims, since they were not using the drug to manufacture a medicament, which is the construct of the Swiss claim.[16]

However, another critical point to be noted here is that the Court indirectly upheld Pfizer`s original demand, that is, a medicament be prescribed listing its brand name. The relevant portion of the judgement is reproduced herein:

The court stated that there was clearly a need for a more organized system than the current one for handling second medical use patents. Justice Arnold, one of the judges in the proceedings before the matter came to the Supreme Court stated that he is convinced more than ever that the best solution to the problem of protecting the monopoly conferred by a second medical use patent while allowing lawful generic competition for non-patented indications of the substance in question is to separate the patented market for the substance from the non-patented market by ensuring that prescribers write prescriptions for the patented indication by reference to the patentee`s brand name and write for non-patented indications by reference to the generic name of the substance.

The abovementioned statement is in contrast to the regulations laid down by the Medical Council of India that drugs be prescribed under their generic name.[17] Further, if the recommendations of Justice Arnold were to be implemented, the affordability and accessibility of repurposed and patented drugs may become an issue even larger than it is today. This may lead to defeating the very objectives of pursuing research to identify a second medical use of a safe drug.

Access to patented molecular libraries

One more major challenge for repurposing drugs is the lack of access to the tens of thousands of molecules synthesized to seek protection for a molecule using a Markush type of claim construct. As only one molecule eventually is approved by the regulatory authorities for marketing, the remaining patented molecules are locked in a 20 year exclusivity granted by the patent. While research exceptions are provided by the patent statutes, an open access to patented molecular libraries should be facilitated, so that more and more molecules that have cleared the bar for safety are available for repurposing.[6,7] Further, there could potential for repurposing the library molecules, but they are commercially unattractive, since they need to be licensed from the patentee to avoid infringement.

A comparative analysis of repurposing patent-in-force drugs Vs patent expired drugs- a COVID-19 induced need

The SARS-CoV-2 virus pandemic brought the focus onto repurposing drugs since an urgent remedy to the situation was being sought. While the pursuit for a vaccine has been more vigorous, the need for a therapeutic remedy cannot be undermined and therefore this is still being actively followed.

Remdesivir was patent protected in India and many other countries and the patent holder, Gilead Sciences, voluntarily licensed the drug to few Indian companies to manufacture and market the drug in India as well in few other countries. The regulatory approval was provided to these companies based on the clinical data submitted by Gilead to the drug authorities. The patents continue to be held by Gilead and they are valid for the next few years. So, in the event the drug is further repurposed, the authorization of Gilead will be required to avoid infringement issues.

On the other hand, the older drugs such as Dexamethasone, Hydroxychloroquine and so on are neither patent protected nor is the clinical data generated for them to treat the virus or any other disease eligible for data protection. So, there is practically no incentive for the pharmaceutical industry to evaluate these drugs for more indications. And this lacuna in our policies and statutes needs urgent attention and redressal to encourage a climate of research for repurposing drugs.

Labelling

As against the skinny label feature of labelling a repurposed pharmaceutical product in Europe, in markets such as India the labelling regulations for pharmaceutical products do not include a mandatory feature that enables detection of a repurposed product. So, the innovator for the second medical use is unable to clearly distinguish the product from that approved for other uses. Inspite of all the aforementioned problems and challenges, there is scientific literature and evidence to show that repurposing can address many more issues than significantly reducing resources

required for drug discovery. It can be a route for finding remedies for those diseases and conditions for which there is not much research being actively pursued or the remedies available are not affordable for the poor patients around the world. A point in case is the issue of antibiotic resistance.

Antimicrobial Resistance and Orphan Diseases

Scientifically it is well established that it takes years of research to develop a new, effective antimicrobial agent that can overcome resistance exhibited by several pathogens. However, there is evidence that several marketed drugs that do not have an anti-bacterial indication can be used along with an antibiotic to kill organisms more effectively or can decrease the Minimum Inhibitory Concentration (MIC) of the antibiotics they are being co-administered with.[18] The use of Ciclopirox and Loperamide against gram negative bacteria and Berberine and Curcumin amongst a few others for activity against gram positive bacteria are a few examples. While Ciclopirox is an anti-fungal agent, Loperamide is approved an as anti-motility agent, Berberine has been traditionally used against diarrhoea caused by gram positive as well as gram negative bacteria and Curcumin is used as a colouring agent, food flavour and nutraceutical. The various methods that can be implemented for repurposing drugs to combat Colistin and Carbapenem resistance in bacteria have also been the subject matter of a study.[19] With the reluctance of the pharmaceutical industry to pursue an active antibiotic development programme, mainly attributed to the ease and speed with which organisms develop resistance to the drug resulting in poor financial returns, the authors opine that repurposing seems to be an attractive route for developing drugs that can overcome the issue of resistant organisms. An exhaustive review of several USFDA approved drugs for combating multi drug resistant pathogens to decrease mortality and morbidity caused by them opines that repurposing can be a quick and economically significant approach to fight bacterial and fungal infections.[20] Similarly repurposing as a more economical route of drug discovery is being continuously explored for addressing Orphan diseases and those diseases that plague third world countries such as multi drug resistant tuberculosis and malaria. Some well-known examples are the use of Tamoxifen, an anti-cancer drug to treat leishmaniasis, Closantel, a veterinary anthelmintic to treat river blindness and the anti-histamine drug, Astemizole to treat malaria.[5]

Proposals and Remedies

Some proposals to remedy the situation of poor protection available to second medical use inventions and their enforceability are in the pipeline and a few of them are listed herein:

New models of drug discovery are being proposed such as government funding for research on repositioning, public-private-partnership models, industry opening up its libraries of molecules to academia to assay for re positioning and few others. The industry has also been working on *in silico* models that can predict the activity for which a molecule can be proposed for repositioning,[5] Also, models are being explored and evidences of molecules binding to multiple targets and eliciting activity are being established and reported.[21]

A strong pitch for the government to make available an alternative type of monopoly protection for new indications, thus providing the appropriate incentives for developing new uses of existing drugs has been observed in literature.[4] The author recommends for the creation of a system to expand the use of e-prescribing, software and electronic medical records for pharmaceutical companies to monitor the prescribed indications when pharmacists fill a prescription. But this may suffer from implementation issues in under developed countries, which are the markets that most need such quicker and more economical alternatives and are also potential markets for the innovator. An example of how counting the number of units sold can be used as an estimation for infringement is described by Roin, however, this will suffer from practical issues of enforceability across various drugs, especially when they are repurposed many times over.[4]

A proposal to use formulation technology for repurposing drugs is described wherein the author opines that a new indication combined with an alternate method of presentation such as novel delivery route minimizes the risk in the repurposing process and also retains commercial value.[22] A similar proposal has been put forth where a new formulation of an active pharmaceutical ingredient with a repositioned drug or a combination of a resurrected or marketed active pharmaceutical ingredient with a repositioned drug to provide the necessary protection through patents is elaborated.[23]

Several schemes and proposals are presented to compensate pharmaceutical innovators for the money spent in drug discovery and for the clinical data generated to seek marketing /regulatory approval.[24] But, till date, most of these plans have not been implemented completely. Therefore, it is difficult to determine whether any one of them work well enough to do away with patenting or data exclusivity provisions. In conclusion, currently multiple routes are still being explored, and no concrete data on their successes are available for a comprehensive assessment.

Recommendations

It is now abundantly clear that repositioning is an attractive route for drug discovery, but lacks effective protection mechanisms and an indisputable and efficient process to prove infringement. An attempt is made here to suggest remedies to the situation to address both these issues.

An amendment to the TRIPs provisions could be attempted, but arriving at a harmonious solution uniformly acceptable to over 150 member countries may become a long-drawn process. Also, amendments to patent laws to mandatorily allow

patenting of second medical use will invite objections and severe criticism, since it is viewed as a route for ever greening of patent rights. In addition, this will call for substantial amendments to definition of patentable subject matter and novelty, which again will be challenging to obtain harmonious consent across the many member countries. A petty patent or a utility patent as implemented in some countries may be considered, but subject matter that is eligible for protection under this law should be novel. Also, the issue of molecules being blocked and their non-availability for further research and commercialization as observed in patenting today, will be a significant issue, defeating the very objectives of a repurposing programme.

A proposal to amend national drug laws, enforced by regional or local drug regulatory authorities may be faster and easier to implement. A data exclusivity period could be proposed for a duration of less than the five years as provided for a New Chemical Entity along the lines of Sec 505(b) of US Food, Drugs and Cosmetics Act. The US Food, Drugs and Cosmetics Act provides a data exclusivity period of three years for a new indication proposed for an existing drug,[12] European Medical Agency too provides a minimum of a one-year additional data protection period for repurposed drugs, if they are proposed within the eight year exclusivity period a new drug is eligible for. The Indian Drugs and Cosmetic Act, 1940 does not provide any such provision for drugs proposed for a second indication.

Data exclusivity is a topic that has been the subject matter of many debates in India, with specific reference to New Chemical Entities. The impact of data exclusivity on public health has been the subject matter of a few studies in India.[25,26]

The Government of India had appointed the Satwant Reddy Committee to review India's position with regard to data protection and to opine on compliance to TRIPs provisions (Report on steps to be taken by GOI in the context of Data protection provisions, 2007).[27] The Art 39.3 of TRIPS states that members should provide for protection of undisclosed test data generated for new chemical entities against unfair commercial use. The Satwant Reddy Committee recommended a calibrated approach towards data protection in India with a period of transition so that the apprehensions of the public and the pharmaceutical industry can be allayed. Quoting from the report, "According to experts like Prof Carlos Correa, a renowned expert in IPR, a chemical entity is deemed new, if there were no prior application for approval of the same drug or where the same drug was not previously known to commerce. It would, however, not apply to new indications, new dosage forms, new combinations, crystalline forms, isomers etc. of existing drugs since, there would be no new chemical entity involved". The Committee`s report has further stated the following:

Data protection cannot be beyond the period of patent protection, Sec 84-92A (Compulsory licensing) and Sec 107 (Bolar exemption) of the Patent Act should override data protection, Generic application can be filed during the period of data protection, and waiver can be allowed in case of public health emergency to grant marketing approval to another applicant.

A key positive note recorded by the report is that the data exclusivity will encourage Indian pharmaceutical companies to conduct research, with special focus on diseases that are prevalent in India and it will facilitate early entry of new drugs into India, benefitting our patients. This is envisioned in the draft Pharma Policy of 2017 of India, wherein the thrust is for the Indian pharmaceutical companies to pursue research collaborating with National institutes and government funded organizations to fulfil the needs of the locals and to treat diseases prevalent in our country.[28] The policy proposes a track where the basic research is carried out in the government labs and the product development is conducted by the industry and the local population benefits. The incentive needed is also provided by the government by way of several schemes under the cause of creating a system of self –reliance. Further, as the industry evolves, we should not be merely the preferred destination of the multinational or global pharmaceutical companies in terms of manufacturing, but we should also be the go-to place for creating valuable products and provide affordable access to much needed medical remedies. As suggested in the Satwant Reddy report, we should initiate data exclusivity through a period of transition and study the impact from different perspectives, then firm up the policy accordingly to proceed for complete implementation.

One route that India can embark on is the initiation of a national level drug discovery programme by pursuing repurposing at the outset before moving to the more challenging novel drug discovery programme. This will enable the industry to develop skills and expertise required to pursue the more vigorous discovery routes. The repurposing route followed initially will also allow the industry to absorb failures more easily, since the investments in a repurposing programme is not as much as in a new drug discovery route. Therefore, India should actively consider a provision of data exclusivity for repurposed drugs and the tenure of the same can be arrived at involving a discussion between the industry and government.

How can a repurposing programme benefit India?

Considering the Indian pharmaceutical industry scenario, where the number of Abbreviated New Drug Applications filed at the USFDA is next only to US companies themselves, the size of the industry is expected to touch $ 55 billion in 2020 and India is considered the pharmacy to the world with exports amounting to $ 20 billion in 2020, the only aspect of the industry where India has not excelled is in creating a pipeline for discovering new drug molecules. A beginning can be made with repurposing, eventually leading to discovering new drugs. The major hurdle today for the Indian pharmaceutical industry is the non-availability of

a mechanism to reclaim the expenditure in conducting clinical trials for repurposed drugs. The exclusivity period suggested herein should provide the necessary stimulus to the industry to innovate with candidates that can be repurposed. Thus, repurposing route also provides an excellent opportunity for Indian pharmaceutical industry to contribute to the Government of India's drive for self-reliance.

In times such as now when we are experiencing continuous waves of the COVID-19 pandemic, an efficient and incentivised repurposing programme has the potential to provide a synergistic effort to the intensive vaccination programme undertaken to relieve the infected population of the morbidity and reduce mortality. Even though a few new molecules are approved for the treatment of COIVD-19, new variants that are resistant to drugs and vaccines are emerging. So, a continuous and committed programme to arrive at efficacious anti-viral drugs–new or repurposed is the need of the day. In the event, any of the new variants cause severe morbidity and/or mortality, repurposed drugs may be the only immediate recourse available.

The issue of infringement has been addressed by proposing an overt or covert feature in the label of a repurposed product enabling an immediate recognition of a repurposed product by a physician and a dispensing pharmacist.[29]

Considering the substantial and numerous advantages repositioned molecules possess, it is evident that a strong protection mechanism and a method to detect infringement without ambiguity would benefit all the relevant stake holders in the system such as the academia, research institutions, pharmaceutical industry, regulatory authorities and most critically the patients. Solutions proposed through various mechanisms should be subject to periodic review to assure the fulfilment of objectives envisaged. The above listed stake holders should be amenable to implement solutions where required. They should also actively consider revisions and amendments to such remedies in accordance to evolving research so that the patients' needs and benefits are always addressed.

In conclusion, a policy to encourage and nurture a paradigm shift in the Indian pharmaceutical industry towards being a drug discovery and drug development entity is imminently required to propel the success of the Indian pharmaceutical industry to attain further development goals. A beginning is possible in this direction by exploring and evolving a new drive towards repurposing drugs for providing remedies to diseases plaguing our populace and also in times such as now of a severe pandemic. Eventually, this can lead to a whole hearted and healthy approach towards regular drug development programmes across the Indian pharmaceutical fraternity.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

ABBREVIATIONS

Sec: Section; **$:** United States dollar; **R&D:** Research and Development; **TRIPs:** Agreement on Trade Related Aspects of Intellectual Property Rights; **GAD:** General anxiety disorder; **US:** United States of America; **UK:** United Kingdom; **INN:** International non-proprietary name; **UKSC:** United Kingdom Supreme Court; **MIC:** Minimum Inhibitory Concentration; **USFDA:** United States Food and Drug Administration; **EP:** European Patent; **GOI:** Government of India; **IPR:** Intellectual Property Rights.

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