SECOND MEDICAL USES FOR EXISTING DRUGS

PATENTS ARE NECESSARY TO INCENTIVISE RESEARCH INTO THIS VITAL AREA OF MEDICINE, WRITE ***PHILIP STEVENS*** *AND* ***JACK ELLIS***

Sometimes, a new or improved medical treatment is closer to hand than we might think. Indeed, many of the drugs available today for the treatment of certain conditions were originally developed to address quite different ailments.

Take, for example, the drug erlotinib – otherwise known by the brand name Tarceva. Originally developed to treat non-small-cell lung cancer, erlotinib was subsequently approved as a treatment for pancreatic cancer.

Beyond this, it has also shown potential as a treatment for cancers of the breasts and ovaries, as well as hepatitis C, psoriasis and type-1 diabetes.

Another instance is zidovudine – also known as azidothymidine (AZT) – a failed cancer medication first synthesized in 1964, but approved two decades later as a treatment for HIV/AIDS. In its new incarnation it formed the backbone of global HIV treatment programmes, extending the lives of millions of patients.

REPURPOSED DRUGS CENTRAL TO THE THERAPEUTIC ARMOURY

Finding new uses for existing drugs is not a rare occurrence. In fact, many important existing drugs have been successfully repurposed (table below).

Table 1: DRUGS THAT HAVE BEEN SUCCESSFULLY REPOSITIONED

DRUG	ORIGINAL INDICATION	NEW INDICATION
Amphotericin B	Fungal infections	Leishmaniasis
Aspirin	Inflammation, pain	Antiplatelet
Bromocriptine	Pakinson's disease	Diabetes mellitus
Finasteride	Prostate hyperplasia	Hair loss
Gemcitabine	Viral infections	Cancer
Methotrexate	Cancer	Psoriasis, rheumatoid arthritis
Minoxidil	Hypertension	Hair loss
Raloxifene	Cancer	Osteoporosis
Thalidomide	Morning sickness	Leprosy, multiple myeloma
Sildenafil	Angina	Erectile dysfunction, pulmonary hypertension

"Repurposing existing drugs holds the key to tackling the many diseases for which there is currently no satisfactory treatment"

Research suggests that up to 15% of given indications for drugs on the WHO's Essential Drugs List were follow-on indications.[1,2] According to some estimates, approximately 90% of medicines most used by patients are approved by the US Food & Drug Administration (FDA) for diseases other than their original approval (so-called "secondary indications").[3]

Repurposing existing drugs holds the key to tackling the many diseases for which there is currently no satisfactory treatment. Carlos Telleria, an expert on ovarian cancer at McGill University in Canada, has written that the repurposing of existing drugs has the potential to "convert cancer into a treatable chronic disease." [4]

Sufferers from the roughly 8,000 rare diseases may also find reprieve, as researchers believe is likely that nearly all these diseases could be

1 'Role of follow-on drugs and indications on the WHO Essential Drug List', Cohen J, Cabanilla L, Sosnov J, 2006
2 'Blocking human fear memory with the matrix metalloproteinase inhibitor doxycycline', D R Bach, A Tzovara and J Vunder, 2017 (http://www.nature.com/mp/journal/vaop/ncurrent/full/mp201765a.html)
3 'Solving the problem of new uses by creating incentives for private industry to repurpose off-patent drugs', Benjamin n. Roin, 2014
4 Carlos M. Telleria, Drug Repurposing for Cancer Therapy, 4 J. CANCER SCI. THER. ix (2012)

treated with drugs that already exist.[5] Drug repurposing also holds real potential for Alzheimer's and many other central nervous system disorders, for which there are currently no effective treatments.[6]

New tools are increasingly available that could revolutionise the way scientists are able to identify existing drugs for repurposing.[7] Historically, new uses for old drugs were revealed through clinician investigation, selective testing of individual drugs in cell-based or animal disease models, or purely through serendipity. But recent advances in chemoinformatics, genomic screening[8] and data mining are changing this into a more targeted, systematic and cost-effective process.

BENEFITS FOR PATIENTS

Repurposing existing drugs makes particular sense for patients. With a repurposed drug, the safety profile is much better understood than for an entirely new medicine. Repurposing a known drug is therefore safer for patients than use of a new drug with little or no track record.

Side effects and drug interactions have already been identified in repurposed drugs, which enables physicians to identify those patients who are likely to encounter side effects, and to make a more informed cost-benefit decision as to whether a drug is appropriate for a specific patient. It will also help physicians understand which drug interactions to avoid.

"That developing a known drug for a repurposed indication would be hugely cheaper than for a single new chemical entity is a common misunderstanding,"

PAINSTAKING R&D REQUIRED TO REPURPOSE A DRUG

Repurposing is not simply a case of changing the packaging and shipping it off to pharmacies. It is almost always the result of extensive research and clinical trials. It is therefore an expensive and risky process that requires appropriate incentives, including patent rights.

In the United States, for example, the FDA prohibits pharmaceutical companies from marketing drugs for 'off-label' uses. And while there is no prohibition on medical doctors prescribing drugs for unapproved indications, obtaining regulatory approval encourages prescriptions for second medical use.

5 Ramaiah Muthyala, Orphan/Rare Drug Discovery Through Drug Repositioning, 8 DRUG DISCOV TODAY THER STRATEG. 71 (2011)
6 Anne Corbett et al., Drug Repositioning for Alzheimer's Disease, 11 NAT REV DRUG DISCOV. 833 (2012);
7 'A Response to Guidelines for Pharmaceutical Patent Examination: Examining Pharmaceutical Patents from a Public Health Perspective', Christopher M. Holman, 2017
8 'Re-Engineering Cures for the Big Data Age: Precision Medicine and Computational Drug Repositioning', Jessica Sagers, 2016

"Without clinical data showing that drug's therapeutic value for the new indication, physicians are much less likely to prescribe the drug for that new use, particularly if it involves an entirely different disease," explains Benjamin Roin, assistant professor of technological innovation, entrepreneurship, and strategic management at the MIT Sloan School of Management.[9] Gaining regulatory approval for a new use also facilities access, by allowing third-party payers to add it to their reimbursement lists.

Of course, setting up and conducting clinical trials is an expensive process, running into tens or even hundreds of millions of dollars. Typically, they take several years to complete, at the very least.[10]

Although the pre-clinical and Phase 1 clinical trial work has already been done for most drug repurposing R&D projects, it is still a major investment taking it through the remaining clinical trials necessary for marketing approval. Patent protection is therefore vital.

"That developing a known drug for a repurposed indication would be hugely cheaper than for a single new chemical entity is a common misunderstanding," says pharmaceutical industry consultant Hermann Mucke. "The most expensive parts of a drug development program, the late-stage trials, apply to a repurposed development, [including of failed drugs] to the same extent."

"Jurisdictions that are home to successful innovative industries offer robust patent protection for new medical uses."

THE ROLE OF INNOVATION INCENTIVES

Thus far, governments and other public agencies have appeared to be largely unwilling or unable to finance drug repurposing R&D.[11] As a result, this significant cost burden has very much fallen on the private sector.

Moreover, new indications tend not to be recognised until long after patent protection has been obtained on the original indication – and often, so long after, that the patent has expired and generic competitors have already entered the market. This means that innovators that have developed drugs for one indication will likely have lost much, if not all, of the market exclusivity offered by the patent on the first medical use by the time that potential second medical uses are revealed.

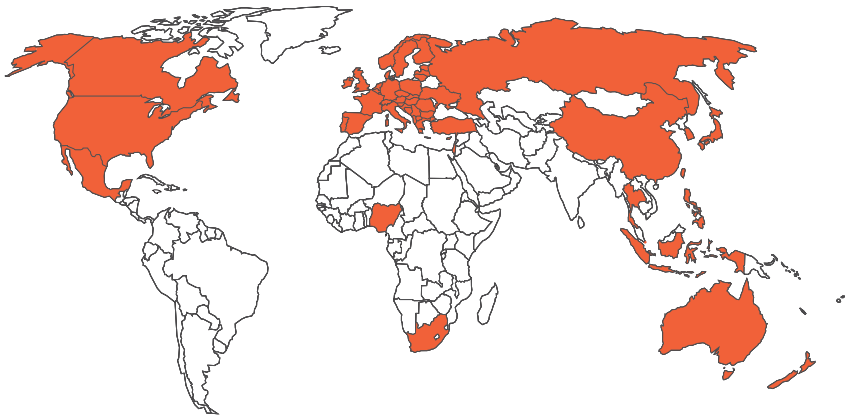
This effectively makes the development process around second indications even riskier, since the diminished patent exclusivity reduces the innovator's opportunity to recoup their R&D spend and secure returns on investment.

9 'Solving the problem of new uses by creating incentives for private industry to repurpose off-patent drugs', Benjamin n. Roin, 2014
10 'Examination of clinical trial costs and barriers for drug development', Aylin Sertkaya, Anna Birkenbach, Ayesha Berlind, John Eyraud, 2014
11 'Solving the problem of new uses by creating incentives for private industry to repurpose off-patent drugs', Benjamin n. Roin, 2014

However, jurisdictions that are home to successful innovative industries mitigate that risk by offering robust patent protection for new medical uses. This is also the reason why several patent offices around the world do grant patents for new medical uses.

The European Patent Office (EPO), for example, has since the 1980s made patent protection available for new uses, in addition to Australia, Canada, China, Japan, South Korea, Indonesia, Israel, Mexico, Nigeria, New Zealand, the Philippines, Russia, Singapore, South Africa, Taiwan, Thailand, Ukraine and the United States.

JURISDICTIONS OFFERING PATENT PROTECTION FOR SECOND MEDICAL USES



INDIA OPPOSED

Not all countries share this view. India does not offer patent protection for new uses of known drugs, with its statutory prohibition in section 3(d) of the Indian Patents Act. This exclusion is based on the notion that new uses do not fulfil key patentability criteria such as non-obviousness and novelty.

But for successful examples of repurposed drugs that deliver genuine benefits to patients, patent protection has been instrumental.

PATENTS SPUR R&D INTO SECOND MEDICAL USE

The drug raloxifene was initially developed by Eli Lilly for the treatment of oestrogen-dependent breast cancer but trials indicated it had a low bioavailability - that too little of the drug made its way into the patient's bloodstream to be effective. However, the perseverance

"These business models help local industries move up the value-chain and in turn generate high quality jobs and sustainable economic growth."

of Lilly's researchers, including extensive clinical trials, eventually revealed new uses for raloxifene, including the prevention and treatment of osteoporosis.

By the time Lilly received FDA approval to market raloxifene for the osteoporosis prevention in 1997, the patent on the drug's original indication had just three years left before expiry.

"Without the incentive of additional patent protection, in this case provided by a method of use patent specifically targeted to use of the compound for osteoporosis, Lilly would have been unlikely to pursue further research once it came to a dead end in its initial breast cancer studies," says Christopher Holman, Professor of Law at University of Missouri-Kansas City University.

Further, a patent validity challenge filed by a generic company failed because the court concluded that given the low bioavailability of the drug, it was not obvious for Lilly's scientists to continue their R&D and develop a successful product.[12]

EMERGING MARKETS' MISSED OPPORTUNITY

The emerging markets that currently deny patent protection to repurposed drugs have much to gain themselves by participating in drug repurposing R&D. It can act as an entry into fully-fledged de novo drug R&D - fledgling companies could undertake proof of concept studies on existing molecules and license them out to more established R&D companies, or alternatively in-license molecules from established pharma companies, screen and validate them, and license them back to the parent companies for development.

These business models help local industries move up the value-chain and in turn generate high quality jobs and sustainable economic growth.

Even though India specifically prohibits patents for second medical uses, many of its companies are increasingly engaged in drug repurposing R&D.

The investment arm of Indian generic behemoth Cipla funds several drug repurposing projects, while Hyderabad-based Dr. Reddy's is pursuing a number of repurposing leads in the dermatology field.[13,14]

"It is not without irony that these Indian companies often choose to make their drug repurposing R&D investments overseas, in countries such as the United States, as their innovations are not eligible for patent protection at home."

12 Christopher M. Holman, In Defense of Secondary Pharmaceutical Patents: A Response to the UN's Guidelines for Pharmaceutical Patent Examination, 50 Indiana Law Review 759 (2017).
13 http://www.drreddys.com/media/40948/investor-day-2015.pdf
14 http://timesofindia.indiatimes.com/business/india-business/Cipla-invests-21-m-in-US-based-co-to-develop-drug-for-Alzheimers-disease/articleshow/35029610.cms

Meanwhile, Indian informatics company Excelra has developed proprietary technology to test known drug compounds for alternative uses. It currently has a strategic partnership with Japan's Astellas Pharma to screen its library of unused drug compounds.

It is not without irony that these Indian companies often choose to make their drug repurposing R&D investments overseas, in countries such as the United States, as their innovations are not eligible for patent protection at home. This harms Indian patients, as these companies are likely to launch first in countries where patent protection is available.[15] For the companies, a major potential opportunity is wasted.

Repurposing existing drugs is an increasingly crucial component of today's drug R&D landscape. For it to reach its full potential, the correct incentives need to be in place to support the significant work that takes place. Recognising this is crucial to building the knowledge economies that will underpin future economic growth in emerging markets and elsewhere.

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15 http://www.livemint.com/Companies/tHyyaF6ja9ZR86YHgd0pMO/DrReddys-gets-FDA-nod-for-antipsoriasis-spray.html