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ASSETS AND LIABILITIES OF DRUG REPOSITIONING

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ABSTRACT

Drug discovery is an awfully tenacious job that takes an enormous amount of time, resources, and money, yet yields unsubstantial results. Drug repositioning is a method for "discovering new uses for old drugs." The main objective to repurpose a drug is to extend the application line of an existing drug, thereby narrowing the productivity gap and at the same time allows a swift reach to the market with high chances of revenues. This approach aims at new formulations, dosage, drug combination, delivery system, alternative pathways and targets, orphan diseases. Likewise the *de novo* drug development, drug repositioning also shares many pros and cons. At one hand, drug repositioning offers relatively less risk-versus-reward ratio; on the other hand, the regulatory authority approval process, intellectual property rights and out-licensing are issues of concern. This review article will particularly focus on the various pros and cons associated with drug repositioning.

KEYWORDS: Chemical databases, Drug repurposing, Intellectual property rights, Off-target drug repositioning, Out-licensing

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INTRODUCTION

Drug discovery within the context of biopharmaceutical industry is an exceptionally competitive field; wherein proper and precise decisions taken on appropriate time, will momentously increase the success of a drug or new chemical entity (NCE) or new molecular entity (NME) launch and contribute to the fruitful revenues as well. It is a known fact that developing an NCE/NME and bringing it to the market is an awfully tenacious job, that undertakes an enormous amount of resources in terms of money as well as time, yet yields unsubstantial results.[1] Apart from this, the biggest challenge is to procure a promising and unique drug candidate in the initial phase of the development (utilizing high-throughput screening, structure-based drug design, combinatorial chemistry); which when placed under clinical trial should have a high certainty of establishing efficacy in the underlying disease/disorder, without compromising the safety. In view of searching a right candidate, technology has provided us with a wide array of tools like cheminformatics, bioinformatics, genomics, proteomics, metabolomics, drug omics data and disease omics data; which can escort us towards the right path for drug discovery and delivering an all new therapeutic option in the market to address the unmet needs of the population at a relatively faster pace.[2] In a normal scenario, the basic drug development process will recognize only 10% of the investigational drugs/molecules finally receiving FDA (Food and drug administration) or respective regulatory authority approval, after spending nearly US $2 billion and 10-17 years at various steps of the developmental process.[3] Because of these anticipated inefficiencies in the *de novo* drug development process, the pharmaceutical industry is looking for alternative approaches that are less time-to consume; at the same moment a less risky endeavor involving only a reasonable expenditure.[4] Thereby, to increase the productivity of biopharmaceutical business, a substitutive method – drug repositioning has recently caught the attention of the pharma corporate world. Drug repositioning is also known as drug repurposing, drug rescuing, drug re-profiling, drug re-tasking and therapeutic switching; it is a method for "discovering new uses for old drugs" or "identification of new therapeutic indications for known drugs."[5, 6] In simple words, it is a second chance for the abandoned drugs or finding a new indication for an existing or approved or failed drugs. The main motive for repositioning is to extend the application line or utilization boundary so as to raise the revenues; additionally, it also shrinks the productivity gap allowing swift reach to the market.[7]Repurposing is also directed to find the treatment for neglected or orphan diseases, as limited resources focus on orphan drug development due to financial constraints. Overall, drug repositioning will aim at (1) formulation, (2) dosage, (3) combination of drugs, (4) delivery systems, (5) known pathways and targets, (6) known therapies, (7) orphan diseases.[8] In other words, it can be summarized as using same therapeutically active ingredient's chemical structure in the original product and re-developing it in order to employ the same active principle to treat different indications.[9] A few famous examples to understand this notion can be stated as – (a) A new twist in thalidomide story; thalidomide, a sedative-hypnotic and anti-emetic drug which was marketed in 1957 in Germany for morning sickness during first-trimester of pregnancy turned into complete disaster and shame for pharmaceutical industry as well as regulatory authorities due to approximately 15,000 children born with severe skeletal deformities. Later thalidomide was withdrawn from the market and a few years later it was profitably repurposed to treat ENL (erythema nodosum leprosum) owing to its anti-inflammatory activity. Soon the utility of thalidomide and its congeners was discovered to cure multiple myeloma, owing to the anti-angiogenic and immunomodulatory properties.[10,11] (b) A promising remedy for sexual dysfunction; sildenafil, a phosphodiesterase-5 (PDF-5) inhibitor was originally tried for angina, subsequentially re-directed to explore its use in erectile dysfunction which was initially reported as a side-effect by volunteers of the clinical trial undertaken for angina. Soon, sildenafil became a blockbuster drug with annual sales reaching billion dollars by 2003 and the same mechanism was applied to pulmonary hypertension.[12,13] (c) A relief from the embarrassing problem in women; duloxetine, a selective serotonin, and norepinephrine reuptake inhibitor, mainly used for depression, proved itself as a pharmacological success in stress urinary incontinence (SUI) where duloxetine exerted central action to increase rhabdosphincter contractility by activating respective pudendal motor neuron 5-hydroxytryptamine – 2 as well as α-1 adrenergic receptors. Earlier, where surgery and pelvic floor muscle exercises were the only options available to treat SUI, duloxetine established itself as leading medical management in SUI.[14,15] The other examples will be subsequently discussed in this review along with briefing of drug repositioning concept, methods available and challenges in re-strategizing existing drugs to new clinical indications.

CONCEPT OF DRUG REPOSITIONING

One of the creative way to develop any existing drug is to re-formulate it; for example:
(1) Modified release formulation – the MMX (Multi MatriX system) formulation of mesalazine compared to oral mesalazine, offers oral once-daily regime providing high dose prolonged-release of drug, additional advantage is of better adherence in patients with mild to moderate ulcerative colitis.[16] (2) Change pharmaceutical form or administration route – oral microemulsion formulation of cyclosporine A demonstrated improved pharmacokinetics in terms of more predictable and steady concentration-time graph compared to already existing oral formulation of cyclosporine A.[17] Changing the route of administration as intravenous for amiodarone to treat resistant ventricular arrhythmia, from oral amiodarone and equating the effects of two different routes on effective refractory period of atrioventricular node.[18](3) Change excipient while retaining same pharmacokinetics – new formulation of Azelastine (anti-histaminic) containing sucralose and sorbitol as excipients to deal with the previously marketed bitter formulation for seasonal allergic rhinitis and non-allergic vasomotor rhinitis; new formulation had similar pharmacokinetics and –dynamics.[19](4) Chiral switching – S-enantiomer escitalopram compared to

racemic citalopram for treatment of major depressive episodes showed faster relief and superiority in response and remission rates.[20] Similarly, S-enantiomer esomeprazole undergoes less hepatic metabolism, obtaining higher plasma concentration and more impressive and adequate decrease in acid secretion as compared to racemic form omeprazole.[21]Another alternative approach utilized by pharmaceutical industry is drug combination, for example – combining two or more antihypertensive drugs (ACE inhibitors, β-blockers, thiazides) into one pill for more efficient control of blood pressure[22]; combining sitagliptin and metformin for better glycemic control[23]; atorvastatin and ezetimibe for hypercholesterolaemia[24]; aspirin and clopidogrel for controlling acute coronary syndrome and ischemic strokes.[25,26] The basis and rationale for drug combination is to provide simple dosing regimen, increased compliance as well as those drugs acting via synergistic mechanism cater more efficient outcomes.[27] Yet another approach to get a better perspective of drug repositioning is "on-target" and "off-target" mechanistic methods. The "on-target" activities are for drugs which are highly selective to a particular target and the pharmacological activity of a distinct drug can be directly linked to a given drug-target interaction; it can be quoted as a molecular target repositioning event. Alternatively, it is a form of "target" repositioning; in this respect, the target has been associated with a new therapeutic area.[28] The various examples can be stated for “on-target” repositioning as: (a) Celecoxib, COX-2 antagonist – originally used for osteoarthritis and rheumatoid arthritis, now alternatively used for adenomatous polyposis[29], (b) Simvastatin, HMG-CoA reductase – originally used as cholesterol lowering agent, substituted as immunomodulatory in treatment of multiple sclerosis[30], (c) Ropinirole, D_2, D_3 dopamine agonist – initially tried as antihypertensive agent, now successfully repositioned for Parkinson's disease and restless leg syndrome.[31,32] The “off-target” activities can be traced to the skewed responses shown by profoundly selective drugs and usually demonstrate activity at a previously unidentified target, those which has been missed by the voluminous panel of investigations done during the developmental stage of a new candidate.[28] There are very few examples to quote here: (a) Telmisartan, an angiotensin type 2 receptor inhibitor – has found it’s potential utility in cardiometabolic disorder including insulin resistance and diabetes as peroxisome proliferator activated receptor-γ (PPAR-γ)-modulating agent[33], (b) Mifepristone, a progesterone receptor antagonist – popularly used as an abortifacient, has shown clinical benefits in Cushing's syndrome[34], (c) Astemizole, a second-generation anti-histaminic drug, have found a new use via successful screening of clinical drug libraryas anti-malarial agent as a sole agent or in combination with chloroquine.[35] Table 1 depicts the novelty associated with different types of drug repurposing.

Table 1
Novelty associated with different type of drug repurposing

	Reformulation, Line extension	On-target Repurposing	Off-target Repurposing	Off-target Repurposing
Indication	Same	Different	Same	Different
Target	Same	Same	Different	Different
Novelty	Low	Some	High	Highest

Another sophisticated way of repurposing drugs is by using computational methods like target-based, knowledge-based, signature-based, pathway-based and targeted-mechanism-based approaches. These methods focus on the various available databases: clinical information, phenotypic screening, chemical information, genomics, proteomics, metabolomics, disease-omics, drug-omics data and apply that knowledge to find out: (a) unknown targets for known drugs, (b) different drugs exhibiting similar action at a known target, (c) new biomarkers for a disease, (d) disease-specific pathways, (e) subtype signaling mechanisms, (f) define unknown mechanisms of drug action.[36]

ASSETS OF DRUG REPOSITIONING

Drug repositioning or repurposing is a very efficient approach for finding new therapeutic indications for already existing drugs. The plus-points to follow aforementioned approach is: firstly, the availability of well-established formulations as well as manufacturing techniques. Secondly, since these approved drugs have undergone stringent evaluation during pre-clinical and clinical studies to prove their efficacy and safety, thereby if that particular drug is applied for evaluation for a new indication, tremendous safety data will be available to support new initiation in drug development. Thirdly, handful information is available regarding the absorption, distribution, metabolism, excretion and toxicity (ADMET) for a molecular entity of interest. Fourthly, the post-marketing surveillance data which is expensive to obtain as well as time consuming is availableat the moment of starting a clinical development program for a new therapeutic indication.[37, 38] Fifthly, when we compare the risk-versus-reward trade-off between divergent drug development strategies (Fig 1), we may find that drug repositioning offers the least risk as compared to individual venture including drug reformulation, in licensing strategies, *de novo* synthesis, and biotechnological development.[36]

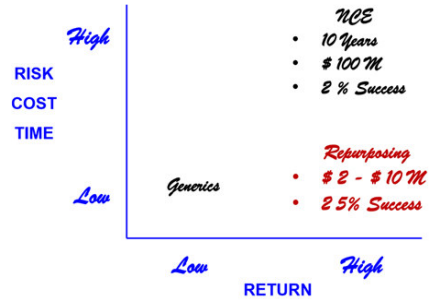

Figure 1
The depiction of the risk, time and cost involved in the development of repurposed drug, NCE, and generic drugs.

Sixthly, in addition to higher rewards, it also allows briefer time to the market with a relatively lesser amount of money and resources spent.[39] Seventhly, drug repurposing is one of the excellent ways for finding therapeutics for rare or orphan diseases. By definition orphan disease, affects a small percentage of a population and no cut-off has been agreed so far to designate a disease as orphan/rare. Though, United States has characterized a cut-off of fewer than 200000 persons affected by a particular disease. As a result of the limited prevalence of a disease and minuscule commercial benefits, less than 5% pharmaceutical industries are interested in spending enormous amount on drug development of an orphan drug. In such scenario, drug repositioning pitches a good offer. In the recent times FDA (Food and Drug Administration) has recognized a 235 drug database of existing approved compounds have shown a promising overture to augment development for orphan/rare indications.[40] Eighthly, the large chemical libraries give a nice proposition to investigate these molecules for diverse drug targets. By utilizing repurposing technology, an integrated approach can be applied to recycle the shelved compounds to new indications. In May 2012, National Center for Advancing Translational Sciences (NCATS) was launched by National Institute of Health (NIH), provide a wonderful initiative that will bring the academic scientists and pharmaceutical industry to revitalize the abandoned drugs.[41] Ninthly, FDA has a distinct approval pathway for submitting a new drug application (NDA) via 505(b)(2) application. This pathway drastically reduces the number of clinical trials required to prove efficacy and safety of a compound which has received one approved indication. On the similar grounds, European countries follow EMEA Article 10 of Directive 2001/83/EC to file an NDA.[42] Tenthly, drug repositioning opens a window for a personalized genomic approach to developing a drug for a particular disease. The databases available for genetic information are dbSNP, Sequence Read Archive (SRA) and Online Mendelian Inheritance in Man (OMIM); when collaborated with drug-omic databases like Connectivity Map (CMAP), Cancer Cell Line Encyclopedia (CCLE) allows to discover best fitted drug for a particular genetic disease prevalent in a particular population.[43]

LIABILITIES OF DRUG REPOSITIONING

Though, this alternative approach to drug development seems very simple, easy and expedite way to fit a compound for a new indication. But as a proverb goes "have patience, all things are difficult before they become easy." There are a lot of liabilities to be faced by the pharmaceutical industry for repurposing a drug, which is a considerable challenge to the advanced facet of innovative repurposing applied science. Some of the challenges can be summed up as follows: (a) Every developmental process requires investment, it might be big or small depending on the product/compound/drug to be established for a new therapeutic venture. Even if the pre-clinical and phase I data might be acceptable to proceed with further phases of clinical trials, it is an expensive and risky endeavor for a relinquished chemical entity. The estimates state the cost for phase III clinical trial exceeds $26000 per patient.[44] (b) How to plan the developmental framework? This is a big question how to formulate a protocol for conducting a clinical trial for a new therapeutic indication with only a handful of information available; what shall be the study population, inclusion, and exclusion criteria, dose administered, treatment duration, novel endpoints, efficacy measures, safety parameters? How much to rely on the information extracted digitally via computation methods involving databases directly to conduct human studies or is it ethical to directly start clinical development without prior animal studies? (c) The R&D (research and development) segment of the bio-pharmaceutical company usually focusses on a distinctive product/compound/drug development and entire resources are concentrated to plan and execute the clinical trial design on a firm proof-of-concept (POC). Thereafter, to divert the expertise and resources to a divergent field of research, demands entirely new setup design, setup, investment and so on.[45] (d) Another issue of concern is the intellectual property (IP) rights of a product/compound/drug. The rights might deal with either COM (composition of matter) or MOU (method of use).[46, 47] The originator will protect their IP on COM (patent on a small molecule, protein, nucleic acid or a formulation) and start a new venture for a different therapeutic indication with the same COM, the developer has to acquire the IP rights from the originator, which in itself is an insurmountable effort.[47] The follow-up innovator may use MOU as repurposing procedure to get approval for phase IV studies in case

the compound has never been granted marketing approval and the developer can acquire off-patent rights for subsequent development of novel MOU.[47] But, to acquire MOU patent for an approved and marketed compound is a backbreaking task, as the new indications are based on physician's observations during routine practice reported as case studies or series; which again has to be assessed in a large population cohort to prove it's validity. Even after successful clinical trial results in terms of efficacy and safety, yet the additional issue is of drug pricing which shall vary for different indications. For example, if an antifungal agent is repurposed to a particular cancerous condition; then the same antifungal drug will have lower price to treat a local fungal infection compared to a relatively higher priced formulation or regimen for respective cancer.[48, 49] (e) Once the repurposed drug gets approval or is in a process of approval by FDA/regulatory authority, concern arises for commercialization and reimbursement. The pharmaceutical sector and investors major focus is strategizing for the market success of repositioned drug to procure a handsome payback on their investment. For example, due to lack of economic incentives companies are not keen to develop drugs for orphan/rare diseases. One side FDA will access "safety and efficacy" of a drug, on the other side investors approach of "vitality and acceptability" of newly marketed drug has to be in equilibrium to achieve optimum fruits of R&D.[50, 51] (f) The exclusivity period of an approved drug is 3 years for new indication, this duration of time is very limited to generate adequate reimbursement. The resisting factors include: existing "off-label" use of a repurposed drug prescribed by the physicians or availability of generic drugs at a cheaper price compared to branded drugs marketed for a new indication. In this regard, an integrated approach has been put forward by WHO (world health organization) called as "Priority medicines for Europe and the world" aimed at harmonized approach, collaborating scientists, physicians, biopharmaceutical industry and patients along with a whole list diseases; favoring government investment in R&D.[52] (g) The pharmaceutical companies are often in search of new ways to out-license their abandoned or shelved molecules which were not able to achieve marketing approval or blocked at certain steps of clinical development. It may be, the originator company may preserve the original rights for the initial indication of drug and out-license the rights for a new indication or out-license the original drug and acquire rights for new indication whatever is of financial interest to the company.[53] The licensing contract should also include buy-back privilege, in case the repurposed drug has a potential to become a blockbuster drug. (h) The investor has to figure out the magnitude of the promising market for a new drug launch; that depends on upon the unmet needs, competition, IP rights, user's/consumer's acceptance and marketing strategy.[53]These issues have to be clearly sorted out from the initiation of development to achieve good dividends at the end.

CONCLUSION

Drug repositioning is not a new concept; nevertheless with the advancement of technology, this field gives a wonderful proposition to discover new indications for existing compounds. From serendipity to strongly determined estimation of drug-target interaction via innovative tools, the field of repositioning/repurposing has grown into a much more refined and matured field of R&D. Research has become slightly apparent due to accessible tools e.g. reagents, chimeric proteins, monoclonal antibodies, aptamers; exceptional measuring tools e.g. real-time pharmacokinetic analysis, multiplexed assays; large databases e.g. bioinformatics, protein sequence databases, genomics, nucleotide sequence databases. Moreover, the well-adjusted relationship between the public-private partnership and governmental funding institutes will further strengthen the repurposing models. It holds a good value proposition for a triad of patients, industry and health care system in terms of providing coverage for unmet medical needs at better therapeutic efficacy, safety, dosing schedule, cost as well as faster access to markets with promising revenues at lesser risks. The power of drug libraries has still to be unleashed to the maximum potential for the benefit of mankind, which can only be achieved by a unified approach involving scientists, physicians, consumers, investors, pharmaceutical industry, government and regulatory authorities.

CONFLICT OF INTEREST

Conflict of interest declared none.

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