Therapeutic Drug Repurposing, Repositioning and Rescue

Part 1: Overview

The pharmaceutical industry is still beleaguered by escalating costs, stagnant productivity and protracted timelines as it struggles to bring therapeutic drugs to market. This situation has been compounded by a ravenous generic drug sector, and patients that have morphed into a discerning consumer population. The growing interest, activity and productivity in Drug Repurposing, Drug Repositioning and Drug Rescue (DRPx) appears to offer some encouragement in finding solutions to the myriad of problems the pharmaceutical companies must overcome. Here we describe the current status of DRPx, discuss the emerging consensus on terminology and describe the tools, technologies and approaches utilised in DRPx. This perspective is augmented by consideration of the companies that provide services and platform technologies for DRPx discovery and development, as well as examples of approved DRPx drugs currently on the market. We also discuss the value and challenges associated with undertaking DRPx and its impact on the pharmaceutical sector as well as patients and the healthcare system.

The litany of problems that beset the pharmaceutical industry continues unabated[1]. The total cost of bringing a new drug to market was recently calculated at a staggering $2.558 billion[2]. Some have argued that this is a gross over-estimation, and a more 'conservative' value is $1.778 billion[3]! The average time required from drug discovery to launch remains at an eye-watering 12-15 years[4]. Approval of new chemical and biological entities, and hence a measure of productivity remains relatively static, but Research and Development (R&D) spending continues to climb[4-6]. Furthermore, stratospheric risk is associated with bringing a drug to market. Initial screening of compound libraries (104-106), leads to a single compound that only has an ~8% chance of successfully traversing the clinical trials gauntlet[7]. Even then, the value and quality of the end product has been questioned, with 'serious concerns raised about the industry's integrity and transparency involving safety and efficacy'[3].

Unfortunately, the 'Wagon of Woe' for pharmaceutical companies does not end once a drug reaches
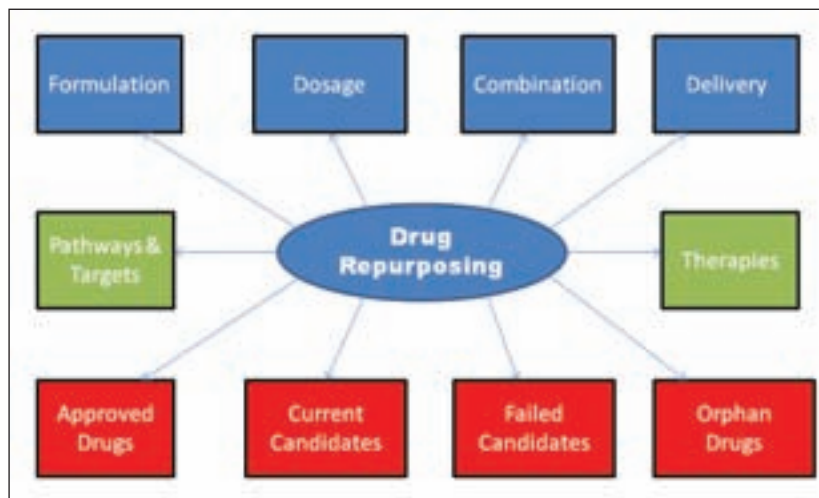
By Dr Stephen Naylor and Judge M. Schonfeld

Definitions of drug repurposing, repositioning and rescue

Currently, DRPx endeavours play an increasing role in the DDD efforts of the pharmaceutical industry. It is estimated that the DRPx process accounts for more than 30% of new drugs and vaccines approved by the US FDA in recent years[13]. In addition Aris Persidis, President and Co-Founder of BioVista, has calculated that DRPx now generates $500 Billion (~25% of annual revenue) for the pharmaceutical industry[14]. This impact has created a flurry of new activity and interest in DRPx. For example, a new journal dedicated to DRPx entitled Drug Repurposing, Repositioning & Rescue has just been launched[15], a book on the subject published[12], a series of annual conferences inaugurated[16] and a workshop sponsored by the Institute of Medicine (National Academy of Sciences) held in Washington DC last year[17].

Unfortunately, the evolutionary process associated with a nascent and/or revitalised discipline is often embodied by chaos, confusion and circumlocution, as evidenced by the similarities experienced in the Biomarker[18] and Companion Diagnostic[19] sectors. Thus, as might be expected, the lexicon of this field is still in flux and there are competing, yet inconsistent 'synonyms' for Drug Repositioning that include Repurposing, Rescue, Retargeting and Reprofiling. More recently there has been a concerted attempt to bring some ontological structure in this area[11,20]. It is now suggested that Drug Repurposing should be used as a catch-all term that includes 'all the redevelopment strategies based on the same chemical structure of the therapeutically active ingredient as in the original product'[11]. Mucke has stated that "repurposing describes the general concept of branching the development of an active pharmaceutical ingredient, at any stage of the life cycle and regardless of the success or misfortune it has encountered so far, to serve a therapeutic purpose that is significantly different from the originally intended one"[20].

Drug Repositioning is defined more specifically as the process of finding a new indication for an approved drug[20]. If the pharmacological framework, such as the pathway or target is the same as for the original indication then it is referred to as On-Target Repositioning. Approximately 80% of Drug Repositioning efforts have occurred through this route. The more novel Off-Target Repositioning is used as the descriptor when the mechanism of action, pathway or target is different from the original indications[12,21]. Finally, Drug Rescue refers to a system of developing new uses for chemical and biological entities that previously

market[8]. Generic drugs continue to offer significant competition, and now capture ~70% of prescriptions written in the USA[3]. Also, 'patent cliff' expirations (2001-2016) have been calculated to cost $245.5 billion in lost sales for the pharmaceutical industry to the generics market[9]. Finally, there is a morphing landscape dictated by more stringent regulatory oversight, demands for mechanism-of-action-based drug discovery and development (DDD) and a patient population driven by the advent of personalised medicine and a consumer mentality[8,10]. This has left the pharmaceutical sector scrambling for avenues of opportunity to minimise risk, reduce costs, and fill their pipelines with safe and efficacious candidate drugs. A series of endeavours that may deliver on addressing such needs include Drug Repurposing, Repositioning, and Rescue. These strategies, and others, have been used in order to combat the current limited productivity of the pharmaceutical industry, and they are all summarised in **Figure 1**[11].

Drug Repurposing, also commonly referred to as Drug Repositioning or Drug Rescue, emerged primarily in the early 1990s as a viable alternative to conventional *de novo* DDD. The terminology (see below) usually refers to the process of identifying new indications for existing drugs, abandoned or shelved compounds and candidates under development. Barrett has noted that "it is an attractive way to maximise return on prior and current preclinical and clinical investments in assets that were originally designed with different patient populations in mind"[12]. In this article we focus on Drug Repurposing/Repositioning/Rescue (DRPx), and do not address drug reformulation, dosage, delivery mechanisms and combination therapies.

were investigated in clinical studies but not further developed nor submitted for regulatory approval, or had to be removed from the market for safety reasons[20].

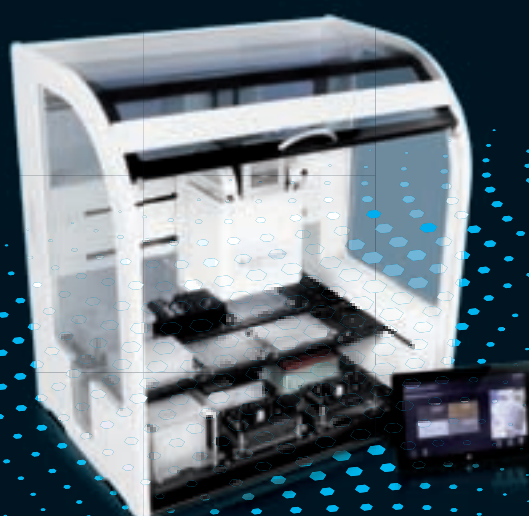### DRPx organisations and initiatives

Most of the larger pharmaceutical companies continue to embrace DRPx efforts in either a formal or *ad hoc* manner. The one exception appears to be Merck. It remains cautious because of the experience with its NSAID Rofecoxib (brand name Vioxx). In 2000-01 the company carried out a series of studies to determine if Rofecoxib was efficacious in slowing down the onset of Alzheimer's Disease, as well as preventing colon polyps (APPROVe Trial). In both these DRPx studies the drug manifested safety issues, including adverse cardiovascular events (APPROVe Trial only). Ultimately, this led to the withdrawal of the drug from the market in 2004[22]. In contrast, other companies, such as Roche, view candidate compounds from a polypharmacological perspective as a potential treatment for multiple diseases. They start out with a rationale for a particular target, but will repurpose during the lifetime of the project if the data indicates a different direction should be taken[23]. Roche formalised its DRPx approach by announcing an arrangement with the Broad Institute in 2012. It agreed to provide 300 of its failed compounds in order to let the Broad Institute screen them for potential new uses[24].

Other large pharma companies that have dedicated internal resources to DRPx include Novartis (New Indications Discovery Unit), Bayer Healthcare Pharmaceuticals (Common Mechanism Research group) and TEVA announced in 2013 the creation of its 'New Therapeutic Entity' initiative. Pfizer, on the other hand, recently closed its DRPx Indications Discovery Unit based in St Louis, but joined the National Center for Advanced Translational Sciences (NCATS) Therapeutic Discovery Program. The NCATS initiative was launched in 2012 and was NIH funded to find new uses for therapeutic compounds shelved or abandoned by pharmaceutical companies. In this programme, eight pharmaceutical companies – AbbieVie, AstraZeneca, Bristol Myers Squibb, Lilly, GlaxoSmithKline, Sanofi-Aventis, Janssen and Pfizer – have collectively made 58 of their compounds available for DRPx. A similar initiative was announced by the Medical Research Council (MRC) in a partnership arrangement with AstraZeneca in the UK. This programme was expanded to include Cancer Research UK late last

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ORGANISATION	CURRENT LEADERSHIP	WEBSITE	LOCATION	FOUNDED	FOCUS AREA
A. Corporations					
Anaxomics	Jose Manuel Mas PhD	www.anaxomics.com	Barcelona, Spain	2013	2,3
BioVista	Aris Persidis PhD	www.biovista.com	Charlottesville, VA, USA	1996	2,3,4
Camargo Pharma	Ken Phelps	www.camargopharma.com	Cincinnati, OH, USA	2003	2
Celentyx	Nicholas Barnes MD	www.celentyx.com	Birmingham, UK	2006	2,3,4
CureHunter	Judge Schonfeld	www.curehunter.com	Portland, OR, USA	2003	2,3
Epsilon 3	Karl Altenhuber	www.epsilon-3.com	Vienna, Austria	2014	1,2
GVK Bio	Manni Kantipudi	www.gvkbio.com	Hyderabad, India	2001	2,3
HM Pharma	Hermann Mucke PhD	www.hmpharmacon	Vienna, Austria	2000	1,2
Kailash BioSciences	Alisa Wright	www.kailashbio	Bloomington, IN, USA	2014	2*
Intellimedix	Jim Richards	www.intellimedix.com	Atlanta, GA, USA	2014	2,3
Marco Polo Pharma	Mondher Toumi MD	www.marcopolo-pharma.com	Paris, France	2008	4
Mellior	Andrew Reume PhD	www.meliordiscovery.com	Exton, PA, USA	2005	2,3,4
nPharmakon	Dmitri Rebatchouk PhD	www.npharmakon.com	Piscataway, NJ, USA	2008	2,3,4
NeXeption	Stephen Tullman	www.nexeption.com	Malvern, PA, USA	2011	5
NovaLead	Supreet Dashpande	www.novaleadpharma.com	Pune, India	2010	3,4
Numedicus	David Cavalla PhD	www.numedicus.co.uk	Cambridge, UK	2008	1,3
NuMedii	Gini Deshpande PhD	www.numedii.com	Palo Alto, CA, USA	2011	3
PharmaKure	Farid Khan PhD	www.pharmakure.com	Manchester, UK	2013	3,4
Quantacea	Ivaylo Penchev	www.quantacea.eu	Sofia, Bulgaria	2012	3
ReDiscovery LifeSci.	Daniel Behr MBA	www.rediscoveryls	Cambridge, MA,	2014	3,4
Revive Therapeutics	Fabio Chianelli	www.revivethera.com	Vaughan, ON, Canada	2012	4
Re-Pharm	Robert Scoffin DPhil	www.re-pharm.com	Cambridge, UK	2011	2,3,4
Seachange Pharma	Nicholas Hodge PhD	www.seachangepharma.com	San Jose, CA, USA	2009	2,3
Sistemic	Jim Reid	www.sistemic.co.uk	Glasgow, UK	2010	2,3
SEEK	Gregory Stoloff MEc	www.seekacure.com	London, UK	2004	4,5
Switch Biotec	Stefan Schulze PhD	www.switch-biotec.com	Conway, AR, USA	1997	3,4
SOM Biotech	Raul Insa PhD/MD	www.sombiotech.com	Barcelona, Spain	2009	3,4
Sosei	Takaya Fujii MBA	www.sosei.com/en	Tokyo, Japan	1990	3,4,5
Therametrics	Raffaele Petrone	www.therametrics.com	Stan, Switzerland	2007	2,3,4
TONIX	Seth Lederman MD	www.tonixpharma.com	New York, NY, USA	2007	4
Transparency LS	Tom Sablinski MD/PhD	www.transparencyls.com	Online presence only	2010	2,4
B. Non-profit					
CWHM	Peter Ruminski MS	www.cwhm.org	St. Louis, MO, USA	2010	2
Cures Within Reach	Bruce Bloom JD/DDS	www.cureswithinreach.org	Chicago, IL,	2005	2,3,6
GlobalCures	Vidula Sukhatme MS	www.global-cures.org	Newton, MA, USA	2004	2
WIPO Re:Search		www.wipo.int/research/en		2011	2
C. Government					
NCATS	Chris Austin MD	www.ncats.nih.gov	Bethesda, MA, USA	2012	2*,6
MRC/AstraZeneca	Chris Watkins	www.mrc.ac.uk	Cambridge, UK	2011	2*,6

year and allows unprecedented access to AstraZeneca's compound library.

A vibrant interest in DRPx has garnered substantial growth in this sector, and resulted in the emergence of a number of dedicated private corporations that are listed in **Table 1**. These companies cover the gamut of capabilities and offer everything from consulting services, such as HM Pharma, to marketed drug products courtesy of NeXeption, SEEK Group and Sosei. Many of the companies listed in **Table 1** provide fee-for-services, offer platform technologies (includes databases and/or technologies) for discovery and development in DRPx, and in some cases have their own pipeline of DRPx compounds.

BioVista is one such company that offers and provides all of these competencies and is widely regarded as a pioneer of dedicated DRPx efforts. The company was founded in 1996 by the Persidis brothers, and has headquarters in both the USA

(Charlottesville, Virginia) and Europe (Athens, Greece). It provides services to the pharmaceutical industry but also has a DRPx discovery platform entitled the Clinical Outcome Search Space (COSS). This computational biology platform intelligently searches a database of pharmacologically active compounds, while simultaneously linking them with mechanism of action, adverse events and human target information. In addition the company has its own DRPx pipeline with candidate compounds in neurodegeneration, epilepsy, oncology and CNS disease. Another company with a robust DRPx pipeline is Therametrics (Stans, Switzerland). It has 19 DRPx pipeline candidates, predicated on its 'unique bio-mathematical technology research platform' which utilises Graph-Network Theory. Based on business and regulatory considerations, they are primarily focused in Orphan Disease areas such as sarcoidosis and idiopathic pulmonary fibrosis, but also have compounds in clinical trials for COPD, Tuberculosis and excessive angiogenesis.

Melior Discovery has taken a more conventional approach to DRPx utilising *in vivo* animal models to determine safety and efficacy of potential drug candidates. It employs approximately 45 validated animal models covering a wide range of disease states. The theraTRACE animal model platform was pivotal in the DRPx discovery of MLR-1023, an oral insulin sensitiser being developed for treatment of type II diabetes. Late last year the company announced that it had received FDA protocol approval for a Phase II trials and also its first milestone payments from its licensing partner Bukwang Pharmaceuticals (Seoul, South Korea). In contrast, Transparency Life Sciences is taking a new, as yet unproven, approach to DRPx discovery and development. It sources its DRPx drug candidates "from the hundreds of distressed clinical-stage compounds that have potential for rescue or repositioning". The approach of the company is based on three principles of; i) crowdsourcing-in order to enable all participant stakeholders to contribute to the design of the company's clinical trials; ii) leveraging advances in information technology and mobile health; and iii) transparency throughout the development process to build credibility with diverse stakeholders. It is attempting to develop a portfolio of drug candidates, retaining ownership stakes in each while soliciting foundations and government grants, crowdfunding, and other potential funding opportunities. At present it is evaluating Naltrexone in Crohn's disease; Lisinopril for multiple sclerosis; Pioglitazone in Parkinson's Disease, Metformin in prostate cancer and Kiacta in sarcoidosis.

Experimental DRPx requires physical access to a collection of approved drugs. In the past this has created considerable obstacles to successful DRPx endeavours. Last year Kailash Biosciences opened its doors and currently offers "480 Smart Compounds of drugs which have regulatory approval for human use and have been selected for their diverse pharmacological properties and their scarcity". Compounds are offered either in a 96-well plate (60 compounds per well) or individual vial format. The company intends to expand its offering to more than 3,600 approved and special interest compounds in 2015. A number of other chemical library companies such as Enzo Life Sciences (Plymouth Meeting, PA, USA), Prestwick Chemicals (Washington DC, USA) and Spectrum Microsource (Gaylordsville, CT, USA) also offer small libraries containing 500-1,000 compounds that are approved or off-patent drugs. (Since these companies offer a suite of other services and products they are not included in **Table 1**.) Also, in 2011 the NIH Chemical Genomics Center pharmaceutical collection was created and a programme initiated[25]. This is a screening service for collaborators to access and assess this approved drug library using a wide range of assays, and thus find new repositioning candidates for a multitude of diseases particularly, rare, neglected and orphan diseases. This effort is now managed by NCATS and the library now consists of ~2,500 approved, small molecule compounds, as well as an additional 1,000 investigational molecular entities.

Corporations are pursuing DRPx efforts for a multitude of reasons but are primarily driven by the need to generate revenues. However, non-profits such as Cures Within Reach (CWR) are pursuing somewhat different goals (see **Table 1B**). Dr Bruce Bloom, Founder and President of CWR, stated that: "Drug Repurposing is a very safe, fast and affordable way to create new medical treatments, especially in those rare and neglected diseases where the economics of new drug development makes it challenging for the for-profit sector, or for the payers."[26] This Chicago-based entity has a broad partnership base consisting of academic and research institutions. It helps finance DRPx collaborative efforts, and has to date facilitated the launch of 10 new DRPx drugs. In 2015 it rolled out its new CureAccelerator Platform. Dr Bloom has stated that "CWR is scaling up the repurposing revolution through the CureAccelerator web platform to find repurposing ideas ready for the clinic, raise the money for the clinical trials, and test the repurposed drugs, devices and nutraceuticals in patients. Then publish the results to give physicians

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DRUG NAME	ORIGINAL INDICATION	NEW INDICATION	YEAR	PHARMA COMPANY
Amitripyline	Antidepressant	Neuropathic pain	2005	AstraZeneca
Amphotericin B	Antifungal	Leishmaniasis	1997	NeXstar Pharma
Aspirin	Inflammation, Pain	Anti-platelet, heart attack, stroke	Various	Various
Azathioprine	Rheumatoid Arthritis (RA)	IBD, MS, organ transplants	Various	Various
Bimatoprost	Glaucoma	Eyelash growth	2008	Allergan
Bleomycin	Antibiotic	Cancer	1973	Kayaku/BMS
Bromocriptine	Parkinson's Disease	Type II diabetes	2009	Novartis
Buprenorphine	Pain	Drug treatment	2002	Reckitt-Benckiser
Bupropion	Antidepressant	Smoking cessation	1997	GSK
		Weight-loss (combi-therapy)	2014	Orexigen/Takeda
Canakinumab	Rheumatoid Arthritis (RA)	Muckle-Wells Syndrome	2009	Novartis
Clofazime	Tuberculosis	Leprosy	1986	Geigy
Colchicine	Gout	Familial mediterranean fever	2009	URL Pharma
Colesevelam	LDL-lowering	Type II diabetes	2008	Daiichi-Sankyo
Crizotinib	Lymphoma	NSCLC	2011	Pfizer
Cycloserine	Tuberculosis	CNS disorders	Various	Various
Cyclosporine	Organ transplant rejection	Psoriasis, RA	1997	Novartis
Dapoxetine	Antidepressant	Premature ejaculation	2004	J&J
Dimethyl Fumarate	Psoriasis	MS	2013	Biogen IDEC
Donepezil	Alzheimer's Disease	Dementia	2006	Eisai/Pfizer
Doxepin	Antidepressant	Atopic dermatitis	2003	Various
Duloxetine	Depression & GAD	Stress urinary incontinence	2004	Lilly
		Fibromyalgia	2008	Lilly
		Pain	2010	Lilly
Eflornthine	Cancer	Hirsutism	2000	Gillette
		Sleeping sickness	1990	Aventis
Etanercept	Rheumatoid Arthritis (RA)	Plaque psoriasis	2004	Amgen/Pfizer
Everolimus	Organ rejection	Various cancers	Various	Novartis
Finasteride	Hypertension	Benign prostate hyperplasia	1992	Merck
		Male pattern baldness	1997	Merck
Fluoxetine	Antidepressant	PMDD	2002	Lilly
Gabapentin	Seizure	Postherpetic neuralgia	2004	Parke Davis
Galantamine	Chronic fatigue syndrome	Alzheimer's Disease	2001	Various
Gemcitabine	Anti-viral	Various cancers	Various	Lilly

the opportunity to determine how they might use these repurposed solutions in clinical practice."[26] The platform connects patient groups, industry, researches and funding sources all interested in the DRPx process, and aims to facilitate the dialogue between them.

In a similar manner, the Center for World Health & Medicine (CWHM) is focused on DRPx candidate compounds, but with interest in neglected and rare diseases primarily impacting patients in Developing World countries. This organisation was founded in 2010 by a group of former Pfizer researchers and access compounds from a variety of sources to evaluate in their pre-clinical models. Currently they have ongoing DRPx projects in childhood diarrhoea, tuberculosis, malaria, sickle cell disease and a number of rare diseases such as idiopatheic pulmonary fibrosis. CWHM is one of a number of non-profit, company and academic groups participating in the consortium World

Intellectual Property Organization (WIPO) Re:Search programme. WIPO Re:Search has created a database of available IP assets including regulatory data, technology and compounds to support research on neglected diseases, and much of this effort is in the form of DRPx investigation. Finally, it should be noted that a number of non-profit patient advocacy and disease foundations support efforts in DRPx focused on their particular area of domain expertise. For example the CHDI Foundation provides guidance, reagents and funding to help companies carry out DRPx activities on candidate compounds as potential therapeutic treatments for Huntingdon disease. While all these efforts are noteworthy, they are usually only a part of other substantial efforts and therefore are not included in **Table 1**.

DRPx is a complex, multi-factorial component process. It requires a myriad of tools, technologies and skilled collaborators to ensure success in the

Table 2 (continued): Drugs approved for new indications after being subjected to DRPx

DRUG NAME	ORIGINAL INDICATION	NEW INDICATION	YEAR	PHARMA COMPANY
Glycopyrronium	Anti-ulcer	COPD	2005	Sosei/Novartis
Histrelin	Prostate cancer	Precocious puberty	2007	Endo Pharma
Hydroxychloroquine	Malaria	Lupus, rheumatoid	Various	Various
Ibuprofen	Inflammation, pain	OA, RA, headache, migraine	Various	Various
Imatinib	CML	GIST	2012	Novartis
		ALL	2013	Novartis
Imfliximab	Autoimmune diseases	Crohn's Disease	1998	Janssen
Iproniazid	Tuberculosis	Antidepressant	1958	Various
Lomitapide	Hypercholesterimia	HoFH	2012	Aegerion Pharma
Methotrexate	Cancer	Psoriasis, RA	2001	Barr Labs
Minoxidil	Hypertension	Hair Loss	1988	Upjohn
Milnacipran	Antideprressant	Fibromyalgia	2009	Forest Pharma
Miltefosine	Cancer	Leishamaniasis	2014	Zentaris
Naltrexone	Opiod/alcohol addiction	Weight-loss (combi-therapy)	2014	Orexigen/Takeda
Onabotulinumtocin	Facial spasm	Cervical dystonia	2000	Allergan
		Chronic migraine	2010	Allergan
		Facial cosmetics	2012	Allergan
Paclitael	Various cancers	Stent restenosis prevention	Various	Various
Paroxetine	Antidepressant	Menopausal hot flashes	2013	GSK
Pertuzumab	Various cancers	HER-2 + breast cancer	2013	Genetech
Plerixafor	AIDS/HIV	Lymphoma & multiple myeloma	2008	Genzyme
Pramipexole	Parkinson's Disease	Restless leg syndrome	2006	Boehringer
Pregabalin	Anticonvulsant, neuropathic pain	Fibromyalgia	2007	Pfizer
Propranolol	Hypertension	Migraine, angina, tremors	Various	Various
Retinoic Acid	Acne	Acute myeloid leukaemia	1995	Hoffman La Roche
Raloxifene	Osteoporosis	Breast cancer	2007	Lilly
Rituximab	Various cancers	Rheumatoid Arthritis	2004	IDEC
Ropininole	Parkinson's Disease	Restless leg syndrome	2005	GSK
Sildenafil	Angina	Erectile dysfunction	1998	Pfizer
		PAH	2005	Pfizer
Sunitinib	GIST and RCC	Pancreatic tumors	2010	Pfizer
Thalidomide	Anti-nausea	Leprosy	1998	Celgene
		Multiple myeloma	2006	Celgene
Zidovudine	Cancer	HIV/AIDS	1987	Burroughs

creation of a 'new' drug. In order to facilitate such efforts a series of Open Source initiatives and models have been created, and some have been described above. This allows for efficient sharing of resources, data, compounds and drugs, compound libraries and screening platforms to "cost-effectively advance old drugs and/or candidates into clinical redevelopment"[27]. Open Source resources continue to be developed and made available and include numerous database and data mining capabilities such as DrugBank, Potential Drug Target Database, Therapeutic Target Database, SuperTarget, PubChem, ChEMBL, ChemSpider, IDMap, Open Phacts and PROMIS-CUOUS. These and other capabilities are described in detail elsewhere[13,27,28].

DRPx discovery – tools & methods

Historically, numerous DRPx drugs have been discovered through serendipitous routes. They include drugs that were tested fortuitously for new indications such as Buproprion (Brand Name Zyban) for smoking cessation, and Thalidomide for leprosy and multiple myeloma. In addition the list includes candidate compounds or drugs where observations of unexpected side-effects in ongoing clinical trials led to the successful development of, for instance, Sildenfil (brand name Viagra) for treatment of erectile dysfunction (ED) and Minoxidil (brand name Rogaine) for hair loss. **Table 2** lists a number of compounds and drugs that were subjected to DRPx efforts and approved for new indications.

A bedrock principle of the pharmaceutical industry used to be the 'one drug-one target' paradigm. However, the high attrition rate of compounds in late stage clinical trials due to poor efficacy indicated that this model was flawed. Today it is clear that 'drug promiscuity', also referred to as polypharmacology, is widespread[29]. Indeed it was

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References

1 PriceWaterhouseCoopers-Pharma 2020. i) The Vision; ii) Virtual R&D; iii) Marketing the Future; iv) Challenging Business Models; v) Taxing Times Ahead; vi) Supplying the Future vii) Introducing the Pharma 2020 Series. http://www.pwc.com/gx/en/pharma-life-sciences/pharma2020/index.jhtml.

2 Cost to Develop and Win Marketing Approval for a New Drug Is $2.6 Billion.Tufts CSDD. http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study.

3 Paul, SM et al. How to Improve R&D Productivity: the Pharmaceutical Industry's Grand Challenge. Nature Reviews: Drug Discovery, 9, 203-214 (2010).

4 Deloitte Centre for Health solutions. Measuring the Return from Pharmaceutical Innovation 2014.Turning a Corner? http://www2.deloitte.com/content/dam/Deloitte/uk/Documents/life-sciences-health-care/measuring-the-return-from-pharmaceutical-innovation-2014.pdf.

5 Gavura, S.What Does a New Drug Cost? Part II The Productivity Problem. http://www.sciencebasedmedicine.org/what-does-a-new-drug-cost-part-ii-the-productivity-problem.

6 Hay, M et al. Clinical Development Success Rates for Investigational Drugs. Nature Biotech. 32, 40-51 (2014).

7 Cook, D et al. Lessons Learned from the Fate of Astra-Zeneca's Drug Pipeline: A Five Dimensional Network. Nature Reviews: Drug Discovery. 13, 419-431 (2014).

8 Naylor, S. NostraPharmus Revisitied:A Future of Splendid Isolation or Multilevel Participation for Pharmaceutical Companies. Drug Discov.World. Summer Supplement, 24-26 (2010).

recently reported that the average drug promiscuity rate is ~6-7.5 targets/approved drug[30]. Such pharmacological properties are a pre-requisite for DRPx efforts to be viable, but it also suggested that a more rational approach to the identification of DRPx candidates is possible. In that regard a variety of tools and technologies have been developed that determine and/or identify: i) compounds that modulate specific disease phenotypes, ii) identify new drug-target interactions, iii) define new roles for existing targets, or iv) find new disease pathways. Many of these technologies were developed and used in conventional DDD, but have also now been routinely applied to DRPx discovery and include high-throughput screening (HTS) and large scale kinase inhibitor assays[12,17,31].

It has been suggested that DRPx discovery should be considered from a drug-centric, target-centric and disease-centric perspective[12,17,21,31]. However, the two predominant outcomes in DRPx discovery are either i) a known candidate compound/drug interacting with a new target, or ii) known target mapping to a new disease indication. Methods and tools utilised in DRPx discovery to identify such possibilities include *in vitro* and *in vivo* (cell/organ/tissue/animal) phenotype model screening, HTS, High Content Screening (HTC), Chemoinformatics, Bioinformatics, as well as Network and Systems Biology[12,13,17,30]. These approaches are used in conjunction with available information on known targets, drugs, biomarkers of disease, and pathways/networks of disease that can ultimately lead to accelerated timelines in the discovery and development of DRPx candidate drugs.

In a thoughtful analysis, Jin and Wong have further sub-classified methods into approaches predicated on available information and elucidated mechanisms[13].The sub-classification of methods consists of:

i) Screening-based: Examples include off-label drug use and phenotype screening. These approaches offer flexibility but typically do not include biological/pharmacological information and do not provide mechanism of action (MOA) insight. Information content output is poor. This includes off-label drug use, phenotype screening using HTS and HCS.

ii) Target-based: examples include HTS, HTC and *in silico* screening of libraries. Targets typically link to MOA, and provide rapid screening capability of compound libraries. Information content output is poor. This includes phenotype screening (HTS/HCS) as well as *in silico* screening (docking and ligand screening studies).

iii) Knowledge-based: examples include various bioinformatic and chemoinformatic approaches. Since the information input is high, the DRPx prediction is more accurate than screening and target-based approaches. Information content output is moderate. This includes drug-target predictions, adverse event reporting, clinical trial information and disease pathway analysis.

iv) Signature-based: Examples include individual gene/protein/metabolite signatures from disease omics data. These approaches are more likely to uncover off-target and disease mechanisms. Information content output is moderate to high. This includes connectivity maps linking diseases with drugs and genome-wide association studies (GWAS).

v) Pathway/network-based: Example includes available signalling or metabolic pathway, and protein interaction networks to reconstruct specific disease pathways. This allows the narrowing down of a large number of proteins to a small specific disease-related network. Information content output is high. This includes differential disease omics and reconstruction of disease pathways to identify key targets.

vi) Targeted mechanism-based: Example includes integrated omics data with signalling pathway and protein interaction networks. This is a powerful approach to delineate MOA for a drug treatment of a specific disease. Information content output is extremely high. This includes determining similarity networks between drugs and disease.

This systematic approach allows one to identify which method to use predicated on the available information. All this is summarised in **Table 3**, and explained in more detail elsewhere[13]. A comprehensive overview and details of existing DRPx methods can be found in a variety of other published works on the subject[12,13,17,21,28,31].

Numerous challenges still exist to execute on cost-effective DRPx efforts. For instance, Jin and Wong stated that: "To test a large number of diseases for a specific drug or a large number of drugs for a specific disease, it is difficult to unify the needed computational approaches because the available information for different diseases or drugs varies. For example, to use target-based methods to reposition drugs for 100 diseases, one would have to know the biomarkers or available pathways for each of these diseases. The knowledge needed for this type of drug repositioning might be unavailable or difficult to derive from the literature or available databases."[13]

However, one DRPx company has taken such an

approach. CureHunter Inc (Portland, Oregon) utilises an Integrated Systems Biology platform which effectively synthesises all the data and knowledge acquired from the methods described above (i-vi screening to targeted mechanism) to produce a clinical outcome database (see **Table 3D**). This database is structured for autonomous prediction of new disease indications for any given drug, biomarker, or active biological agent. The platform consists of five modules:

i) Controlled source knowledge module: US National Library of Medicine archive (USNLM) from 1809-current (continuously updated).
ii) Data acquisition module: High precision clinical efficacy variable text mining capability using a purpose-built semantically intelligent Natural Language Processor.
iii) Array module: All data is arrayed into a drug-disease-outcome relationships database where each relation is an empirically weighted contributor to clinical efficacy.
iv) Analysis module: Using Network Graph Theory and a suite of algorithms to determine the most centric and similar components of clinical efficacy for all diseases.
v) Prediction module: Answer system analytics automation layer with graphic user interface (GUI) for real-time output of new indications with high probability of clinical success prediction.

The CureHunter platform facilitates the capture and automated DRPx analysis of all of published biomedical knowledge (in the USNLM) demonstrating a functional role in the clinical efficacy potential of more than 250,000 active biological molecules, markers, mechanisms and drugs operating in more than 11,600 disease states. Each year this self-updating system has added close to one million new records to its master clinical outcome database so that the system constantly learns and updates its predictive analyses in real time. Thus the design and operation of the CureHunter engine also solves one of the major problems facing the DRPx community, namely the need to cost-effectively utilise the ever-increasing flow of data and forward integrate new research for successive years of discovery. It is interesting to note that the system is effectively a 'push-button' DRPx engine.

DRPx drugs

Approximately 80 examples of DRPx drugs have been approved and launched as therapeutic agents for new indication(s) in the USA and Europe[32]. The origin of such DRPx candidates is varied but

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FIELD TYPE	METHOD/CATEGORY	APPROACHES USED/OUTPUTS
A. Drug-centric		
Off-Label	Blinded serendipity	Clinical decision
Phenotype screen	Blinded screening	HTS/HCS
Phenotype screen	Target-based screening	HTS/HCS
Chemical structure	Target-based chemoinformatics	In silico screening
Drug-target interactions	Knowledge-based bio/chemoinformatics	Drug-target predictions
Clinical trials data (adverse events)	Knowledge-based bioinformatics	Correlation analysis for drug similarity
Approved drug-adverse event	Knowledge-based bioinformatics	PCA for drug similarity
B. Target-centric		
Pathways	Knowledge-based bioinformatics	Disease mechanism
Omics data	Signature-based bioinformatics	Primarily gene signatures
Genetics data	Signature-based bioinformatics	GWAS
Pathway/omics data	Pathway/network biology	Disease pathways
C. Disease-centric		
Drug omics data	Signature-based bioinformatics	Connectivity maps
Drug omics data	Signature bioinformatics/networks	Gene signature & community structure
Disease/drug omics data	Signature-based bioinformatics	Differential signatures
Drug omics, disease pathway & protein interaction networks	Target mechanism-based & network biology	Target pathway elucidation
D. Clinical outcome-centric		
Drug/omics/pathway/networks & systems	Target mechanism-based & disease pathways/networks	Differential clinical outcome database
Patient reportage	Web & EMR-based	Association databases

can be loosely grouped into one of the following categories: i) Compounds from academic and public sector labs that were never commercialised; ii) Compounds already in a clinical development that demonstrated polypharmacology; iii) Shelved compounds – failed to demonstrate efficacy in Phase II or III clinical trials; iv) Drugs that were discontinued for commercial or safety reasons; v) Drugs close to patent expiry or competition from generics; vi) Drugs with incremental new indications-known as Line Extension; vii) Drugs available in developing markets but not commercialised in the USA/Europe/Japan (sometimes referred to as Geographical/Transnational DRPx).

A poster-child for DRPx, and an example of a shelved drug candidate, is Sildenfil. This compound is a potent inhibitor cGMP-phosphodiesterase 5, an enzyme known to regulate blood flow. Sildenfil was being evaluated in clinical trials for the treatment of angina. However, the trials were suspended after it was demonstrated that the compound manifested pharmacokinetic properties that were inconsistent with the prolonged control necessary for the treatment of angina. By happenstance, during the

clinical trial, researchers noted an unexpected side-effect that led to the development and approval of the compound for previously untreatable, erectile dysfunction (ED) in 1998. Ironically, the original 'poor' pharmacokinetic properties of Sildenfil actually made it an ideal drug for ED therapy. Subsequently, Sildenfil was also found to be effective in the treatment of pulmonary arterial hypertension and was approved for use in the USA in 2005, but is marketed under the brand name REVATIO. Other examples of drug candidates that lacked efficacy in the original clinical trial but were successfully repurposed include Canakinumab, Pertuzumab and Finasteride. In the case of Finasteride, this was originally evaluated for hypertension, but was ultimately repurposed for both benign prostate hyperplasia (BPH) as well as male pattern baldness (MPB), and in both cases was an on-target repurposing endeavour. **Table 2** provides a summary of this data as well as a list of other approved DRPx drugs that includes their original indication and new indication(s).

A limited number of drugs have failed after their post-market launch, but then subsequently subjected to successful DRPx. The most well-known example of such a strategy is the 'notorious' drug Thalidomide. It was originally marketed as a sedative and antiemetic and had an inhibitory effect on morning sickness, common in pregnant women. Unfortunately, the drug had a teratogenic effect on the foetus and many children were born with deformed limbs and faces. The drug was withdrawn from the market in 1962. Further studies revealed that the drug also appears to inhibit Tumor Necrosis Factor-Alpha signalling and it was subsequently approved for the treatment of erythema nodosum leprosum, a painful skin condition of leprosy in 1998 and Multiple Myeloma in 2006. The drug is currently under evaluation for an additional 30 other new indication treatments.

As discussed above, drug promiscuity is now well-recognised, and any one drug can affect more than a single pathway, which can ultimately lead to new indications for drug candidates or existing drugs. Thalidomide is an example of off-target DRPx. Other drug candidates that have been subject to successful off-target DRPx include Crizotinib and Imatinib. Crizotinib is a protein kinase inhibitor that binds within the ATP-binding pocket of target kinases. It was originally tested for anaplastic large cell lymphoma as a MET-kinase inhibitor. However it was subsequently approved by the FDA in 2011 for the treatment of non-small cell lung cancer where the ALK-oncogene was the target. In addition, Imatinib (brand name Gleevec),

a small molecule BCR-abl tyrosine kinase inhibitor, was originally approved for treatment of chronic myelogenous leukemia (CML). The drug was further approved by the FDA in 2002 for use in patients with gastrointestinal tumours (GIST), and again in 2012 for removal of KIT-positive tumours after surgery in order to prevent the reoccurrence of the tumour. In both cases the MOA involved off-target c-kit and PDGF-RA.

There are numerous examples of on-target DRPx, and include such popular drugs as Duloxetine (brand name Cymbalta), Everolimus (brand name Zortress), Sunitinib (brand name Sutent) and the first anti-retroviral Zidovudine (brand name Retrovir, also known as AZT). Sunitinib is an example of a drug-centric DRPx case. The drug was originally approved for treatment of GIST and renal cell carcinoma (RCC) as a receptor tyrosine kinase inhibitor. It was subsequently subjected to DRPx and approved for treatment of pancreatic neuroendocrine tumour in 2010. Everolimus is an example of a target-centric approach. This drug is used as an immunosuppressant in the post-treatment of organ transplant patients, and inhibits the mammalian target of rapamycin. The target was subsequently identified as an important candidate in numerous other diseases and the drug was approved for kidney cell cancer (2009), astrocytoma (2010), metastatic pancreatic neuroendocrine tumour (2011) and HER-2(-) breast cancer (2012). As an interesting aside, the compound was also approved for use in conjunction with a drug-eluting stent as an immunosuppressant to prevent restenosis. Duloxetine is a reported example of a DRPx where the pathway was determined to be important in other diseases. The drug is a mixed serotonin/norepinephrine reuptake inhibitor (SNRI.) It was initially approved for the treatment of depression and general anxiety disorder (GAD), but was repurposed for fibromyalgia (2008) and musculoskeletal pain (2010). However, the pathway and mechanism of action for its analgesic properties has subsequently been suggested to act via a sodium channel blocker and not the SNRI pathway[34]. A final example of an on-target DRPx effort involves Zidovudine. This drug is a nucleoside analogue reverse-transcriptase inhibitor that was subjected to DRPx and became the first antiretroviral approved for the treatment of HIV/AIDS. It was originally evaluated as an anticancer agent in the 1960s, since the prevailing theory at the time was that most cancers were caused by environmental retroviruses. Needless to say the original cancer testing proved to be unsuccessful.

9 Accenture Life Sciences. Beyond the Patent Cliff-Signs of Recovery in BioPharma's New Normal. http://www.accenture.com/Site CollectionDocuments/PDF/Ac centure-Life-Sciences-Beyond-The-Patent-Cliff-Signs-Of-Recovery-in-Biopharmas-New-Normal.pdf.
10 Kessel, M. Restoring the Pharmaceutical Industry's Reputation. Nature Biotech. 32, 983-990 (2014).
11 Murteira, S, Ghezaiel, Z, Karray, S and Lamure, M. Drug Reformulations and Repositioning in Pharmaceutical Industry and its Impact on Market Access: Reassessment of Nomenclature. Journal of Market Access & Health Policy 1: 21131 – http://dx.doi.org/ 10.3402/jmahp.v1i0.21131 (2013).
12 Barratt, MJ and Frail, DE (Eds). Drug Repositioning: Bringing New Life to Shelved Assets and Existing Drugs. John Wiley & Sons, Hoboken, NJ, USA. (2012).
13 Jin, G and Wong, STC. Toward Better Drug Repositioning: Prioritizing and Integrating Existing Methods into Efficient Pipelines. Drug Dis. Today 19, 637-644 (2014).
14 Persidis, A. Personal Communication. Data to be published in Drug Repurposing Rescue & Repositioning. (2015).
15 Persidis, A and Mucke, HAM (Eds). Drug Repurposing, Rescue & Repositioning. http://www.liebertpub.com/ove rview/drug-repurposing-rescue-brand-repositioning/627.
16 Lederman, S. Drug Repurposing Rekindles Promise. GEN. January 30th 2013. http://www.genengnews. com/gen-articles/drug-repurposing-rekindles-promise/4710/?kwrd=Drug%20 Repositioning.

17 Beachy, SH, Johnson, SG, Olson, S and Berger, AC (Eds). Drug Repurposing and Drug Repositioning-Workshop Summary. National Academies Press, Washington DC, USA (2014).

18 Naylor, S. Overview of Biomarkers in Disease, Drug Discovery and Development. Drug Discov. World. Spring Edition: 21-30 (2005).

19a Naylor, S and Cole, T. Overview of Companion Diagnostics in the Pharmaceutical Industry. Drug Discov. World. Spring Edition: 67-79 (2010). **b** Naylor, S and Cole, T. Companion Diagnostics in the Pharmaceutical Industry: Part II Business Models Drug Discov. World Summer Edition: 61-68 (2010).

20 Mucke, HAM. A New Journal for the Drug Repurposing Community. Drug Repurposing, Rescue & Repositioning 1, 3-4 (2014).

21 Sekhon, BS. Repositioning Drugs and Biologics; Retargeting Old/Existing for Potential New Therapeutic Applications. J. Pharm. Educ. Res. 4, 1-15 (2013).

22 Sukkar, E. Still Feeling the Vioxx Pain. Pharm. J. September 14th, 2014. http://www.pharmaceutical-journal.com/news-and-analysis/feature/still-feeling-the-vioxx-pain/20066485.article.

23 Thayer, AN. Drug Repurposing. Chem. & Eng. News 90, 15-25 (2012).

24 Fierce Biotech. Roche and Broad Band Together to Bring Failed Drugs Back from the Dead. http://www.fierce biotech.com/story/roche-broad-band-together-bring-failed-drugs-back-dead/2012-11-28.

25 Huang, R et al. The NCGC Pharmaceutical Collection: A Comprehensive Resource of Clinically Approved Drugs Enabling Repurposing and Chemical Genomics. Science Translational Medicine 3, 80ps16.doi:10.1126/scitranslmed.3001862 (2011).

Value and challenges of DRPx

The tribulations of the pharmaceutical industry have been discussed already in this article. The development and successful execution of well thought-through DRPx strategies can help alleviate such problems and add significant value to pharmaceutical company pipelines as well as to patients, the ultimate end-users of these products. The specific issues that contribute to DRPx value include:

i) Cost savings: Previously, Persidis has suggested that the cost "to relaunch a repositioned drug averages $8.4 million"[35]. This appears to be a rather conservative estimation and may be more applicable to simple, line-extension DRPx cases. We estimate that the cost is ~$300 million, assuming that the DRPx candidate has to undergo Phase II and Phase III clinical trials. This is predicated on the model proposed by Paul et al[3], but still represents an ~85% saving, compared to the $1.778 billion cost of a *de novo* DDD drug.

ii) Time savings: A commonly-cited assumption is that DRPx can reduce the conventional DDD process by 3-5 years. We estimate a cycle time of ~6.5 years for a DRPx drug, again based on the model of Paul and co-workers[3]. However, there are examples of even more rapid DRPx approvals. Crizotinib was investigated as a DRPx drug based on its ALK-inhibiting properties. It was approved for the new indication of NSCLC treatment in just four years[31].

iii) Productivity/risk: The attrition rate of drug candidates subjected to the conventional DDD process is ~95%. Much of this failure is caused by a compound's lack of safety (~45% failure in Phase I) and efficacy (~65% failure rate in Phase II)[3]. These poor success rates place tremendous pressure on the drug pipeline and hence pharmaceutical company productivity. Since DRPx drugs have been either approved or shown to be safe in late stage trials, they can enter the pipeline at the efficacy stage, thus significantly decreasing the failure-rate probability and increasing the chances for a successful launch. It has been reported that 25% of DRPx drugs successfully make it from Phase II to market launch in contrast to only 10% for conventional DDD drugs. The probability of success increases to 65% for DRPx drugs moving Phase III to market (only 50% for DDD drugs)[23]. In addition it is estimated that there are at least 2,000 failed drug candidates available that could be exploited through a DRPx strategy, and this number increases by 150-200 compounds per year, providing an ample pipeline of opportunity[36].

iv) Market potential: The market potential for a DRPx drug is determined by the same market forces as a conventional DDD drug and includes drug differentiation, market need, patient acceptance, marketing strategy and Intellectual Property (IP) position[35]. Thus a DRPx drug has the same possibility to achieve blockbuster status as a *de novo* derived drug. A recent example of a DRPx blockbuster drug is dimethyl fumarate (brand name Tecfidera) from Biogen IDEC. It was approved for a new indication to treat multiple sclerosis (MS) in 2013 and achieved revenue sales of >$2.5 billion worldwide in 2014. This represented ~30% of total revenues for Biogen IDEC last year.

v) Intellectual Property: DRPx can help in patent life elongation and thus aid in prolonging lifecycle management of product portfolios. Persidis has argued that a successful DRPx strategy can significantly cushion the patent cliff dilemma faced by the pharmaceutical industry[35]. In part this can be achieved because it is possible to "obtain very strong patent protection for a new use of an existing drug whose composition of matter patents are still running, if that new use is not covered and proven in the original patent".

vi) Patient/health system: The advent of personalised medicine has fuelled the transition of patients to consumers[19b]. This has led to a more demanding customer-base that requires a better, cheaper, personalised product. DRPx efforts have impacted significantly on orphan, rare and neglected diseases[12], as well as providing therapeutic efficacy where none existed previously (eg Sildenfil). Consumer needs, in the form of cheaper, faster, safer, more efficacious drugs across the entire drug spectrum, are being considered and contemplated with the more widespread adoption and use of DRPx.

On the other hand it is also important to recognise that DRPx still requires an element of discovery and development. These undertakings bring inherent risk and it is important that one comprehensively understands the science, disease, patient population, regulatory, business and IP issues associated with any specific DRPx initiative. For instance, new Phase I clinical trials may be required if the DRPx candidate is an old drug and the original safety data does not meet current regulatory standards. Plus, safety issues can still present problems for a potential new indication. For example, Buproprion, a drug originally approved for the treatment of depression, was subject to DRPx efforts in the treatment of obesity. These studies involving the individual drug were ultimately unsuccessful due to adverse events observed in the clinical trials[31]. However, the drug was ultimately

approved as a combination therapy with Naltrexone in late 2014 and is marketed under the brand name Contrave (see **Table 2**).

Another obvious challenge is that the efficacy of a DRPx drug must be demonstrated. Clearly the DRPx drug must have superior, differential properties from existing drugs already being marketed and sold in the same class. Otherwise it will be subject to the same regulatory scrutiny as a conventional drug, which could have a significant impact on its forward progress. Any lack of differentiation or clear efficacy can obviously lead to the DRPx trial being abandoned. For example, Sunitinib was originally approved for treatment of GIST and RCC, but failed in a multitude of other cancer trials due to efficacy issues[31]. A final consideration of obstacles and hurdles that can confront the unwary is IP and (original) drug ownership issues. These can be complex and troublesome as one attempts to navigate the DRPx process. Such issues, as well as business and regulatory matters, will be considered and discussed in detail in our subsequent manuscript on this subject[37].

Conclusions

The continued rising costs, combined with the catastrophic failure rates of *de novo* DDD have driven the pharmaceutical industry towards some exploration of DRPx strategies and their potential. This has been augmented somewhat by the well-documented problem of the 'Patent Cliff', as well as the more aggressive stance taken by Generic companies as they look to infiltrate the conventional DDD sector. However, implementation of a successful DRPx strategy is not a simple undertaking. The skills and expertise required are considerable and range across a number of different disciplines. They include the need to access compounds and information, determine the disease area of focus and implement a well thought-through business and IP strategy. The successful execution of a DRPx business model can result in a pipeline that has an increased number of Phase II-level compounds, as well as lead to new innovations in disease aetiology and pathway/network biology. It can also address what Persidis labels the competitor adjacency threat. He was recently quoted as

Continued from page 60

26 Bloom, B. Cures Within Reach. Personal Communication.

27 Allarakhia, M. Open source Approaches for the Repurposing of Existing or Failed Candidate Drugs: Learning From and Applying the Lessons Across Diseases. Drug Design Develop. Ther. 7, 753-766 (2013).

28 Loging, W. Cheminformatic/Bioinformatic Analysis of Large Corporate Databases: Application to Drug Repurposing. Drug Dis. Today 8, 109-116 (2011).

29 Haupt, VJ, Daminelli, S and Schroeder, M. Drug Promiscuity in PDB: Protein Binding Site Similarity Is Key. PLoS ONE 8, (2013). http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0065894.

Drug Discovery

30 Hu, Y and Bajorath, J. Monitoring Drug Promiscuity Over Time. F1000Research 3, (2014), Last updated: 05 JAN 2015. http://f1000research.com/articles/3-218/v2 .

31 Li, YY and Jones, SJM. Drug Repositioning for Personalized Medicine. Genome Medicine 4, 27-41 (2012).

32 Murteira, S, Millier, A, Ghezaiel, Z and Lamure, M. Drug Reformulations and Repositioning in the Pharmaceutical Industry and Their Impact on Market Access: Regulatory Implications. Journal of Market Access & Health Policy 2, (2014) http://dx.doi.org/10.3402/jmahp.v2.22814 .

33 Padhy, BM and Gupta, YK. Drug Repositioning: Re-Investigating Existing Drugs for New Therapeutic Indications. J. Postgrad. Med. 57, 153-60 (2011).

34 Wang, S-Y, Calderon, J and Wang GK. Block of Neuronal Na+ Channels by the Antidepressant Duloxetine in a State-Dependent Manner. Pain Medicine 113, 655-665 (2010).

35 Persidis, A. The Benefits of Drug Repositioning. Drug Discov. World Spring Edition: 9-12 (2011).

36 Knowledge-Based Drug Repositioning to Drive R&D Productivity. Thompson Reuters (2012). http://thomsonreuters.com/products/ip-science/04_038/drug-repositioning-cwp-en.pdf.

37 Naylor, S, Kauppi, DM and Schonfeld, JM. Therapeutic Drug Repurposing, Repositioning, and Rescue: Part II- Regulatory, Intellectual Property and Business Considerations. Drug Discov. World In Press (2015).

38 See Sirk, K. Everything Old is New Again. Drug Discov. News 10, (2014). http://www.ddn-news.com/index.php?newsarticle=6045.

stating that: "Competitor adjacency threats drive companies to not only add new compounds to their pipelines, but indicate when a savvy company reacts to what its competition is doing with a new twist on an old compound."[38]

There are numerous factors that contribute to the feasibility and viability of DRPx. They include access to voluminous amounts of scientific and clinically curated data, the large number of potential drug candidates that could be made available, lead time from proof-of-concept to Phase II is short, and infrastructure needed to undertake DRPx can be limited. The future appears bright for DRPx, but there are a number of issues impacting the future that need to be considered and include; i) how to maximise the generation of ideas through open source partnerships that includes academia, industry, non-profits and government agencies; ii) better design of clinical trials and patient selection; iii) electronic medical records need to be more fully integrated into the study of patient outcomes and therapeutic effectiveness as well as utilised in a systematic role in DRPx selection processes; iv) key stakeholders such as FDA/EMA, payers, patient advocacy groups should play a more substantial role; and vi) automation and updating capability should be key review factors for commercial organisations seeking to prioritise adoption of DRPx methods and stay competitive over time. Highly automated semantically intelligent systems can reduce data capture errors and bioinformatics workloads dramatically.

The numerous benefits of DRPx are clear and well documented[12,17,35]. If this is so transparent then why is the pharmaceutical industry so slow on the DRPx uptake and in many cases only practicing on an *ad hoc* basis? It is possible that the entrenched, silo-structured, pharmaceutical companies are not conducive corporate structures for DRPx. In addition there appears to be a sentiment that DRPx is not an endeavour that produces innovative research and outcomes[35]. Such attitudes need to change and the pharmaceutical industry needs to be more embracing of this exciting, innovative and productive series of approaches. Wide-scale implementation of smart DRPx strategies could unleash a torrent of productive activity that enhances pharmaceutical company performances and provides significant opportunities for all the stakeholders including the public and private sectors as well as those 'demanding' patients!

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