Therapeutic Drug Repurposing, Repositioning and Rescue

Part II: business review

There is an emerging consensus that the impact of Drug Repurposing, Repositioning and Rescue (DRPx) on the pharmaceutical industry is real and sustainable. The activity and productivity of DRPx focused companies as well as pharmaceutical company efforts appear to offer some encouragement in providing solutions to the myriad of problems the industry faces at the present time. These efforts can only be sustained and expanded if the dynamic variables of viable and creative business models are identified and understood. In this work we describe the lessons that can be learnt from surveying the landscape of the DRPx industry. This analysis includes both the successes and the failures of past DRPx companies. We introduce the various stakeholders that are shifting the decision process of DRPx implementation and acceptance away from the pharmaceutical industry. In addition the component pieces necessary to enhance the value of a DRPx company are discussed and the top 10 mini-blockbuster and blockbuster DRPx drugs are introduced. Finally, we assess and compare an assortment of DRPx business models and evaluate the current climate of the DRPx industry.

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A confluence of pharmaceutical company intransigence and conservatism has conspired to increase drug discovery and development (DDD) cost, cycle time and risk. This trifecta of woes has been exacerbated by aggressive generic drug company activity and on-going 'patent cliff' losses. The consequences have been a stagnant industry pipeline and a decrease in revenue-generating products, which, in turn has resulted in significant R&D personnel lay-offs. This prolonged lack of pharmaceutical productivity and stifled innovation has coincided with demands for faster delivery of better, safer and cheaper drugs by patients and healthcare systems. These drugs must be effective in the prevention and treatment of the panoply of diseases, from lifestyle-

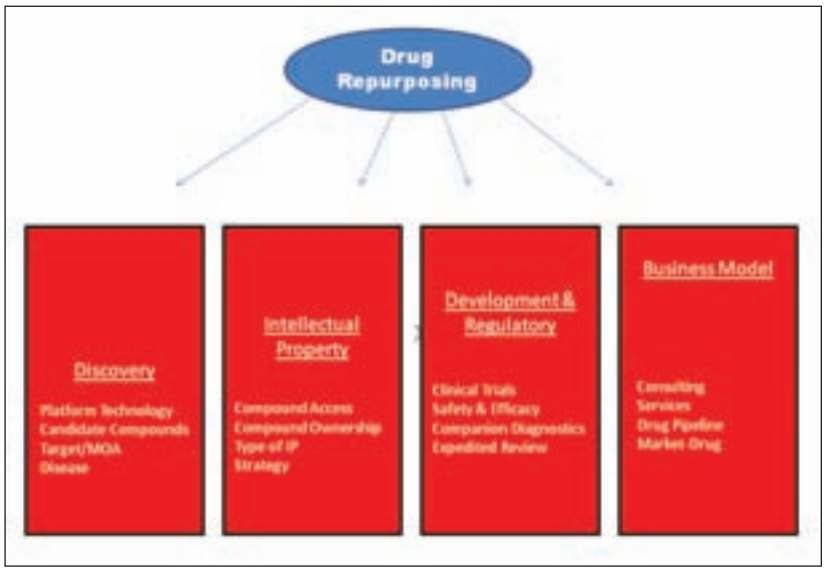

Figure 1
Factors that must be considered in the discovery, development, IP, regulatory and business model processes of a DRPx company

related illnesses, to rare/orphan and neglected maladies. Such entreatments on an anaemic DDD industry pipeline have resulted in the pharmaceutical and biotech sectors considering a variety of approaches to alleviate this conundrum. In that regard we have stated previously that "widescale implementation of smart Drug Repurposing, Repositioning and Rescue strategies could unleash a torrent of productive activity. This should enhance pharmaceutical company performances and provide significant opportunities for all the stakeholders, including the public and private sectors as well as [end-user] patients"[1].

At present there is a flurry of activity in Drug Repurposing/Repositioning/Rescue (DRPx). Pharmaceutical and boutique DRPx companies are utilising and evaluating such approaches as cost and time-effective strategies to significantly reduce DDD risk[1]. DRPx can result in new sales and market opportunities for shelved or abandoned compounds/drugs and during their exploration can reveal major new mechanisms of action relative to new target disease indications that may also lead to Intellectual Property (IP) claims. Such efforts can also extend the life of current, marketed drugs by determining new indications and/or formulations. The commercial success, however, of any DRPx endeavour depends on a myriad of factors and this is captured and summarised in **Figure 1**. This includes all the component parts of the DRPx discovery process, IP and regulatory issues pertaining to the clinical trials and the most suitable business models. In particular, repurposed/reposition/rescued drug (RRRDx) market exclusivity is of paramount importance and can be adequately achieved by a combination of thoughtful IP and regulatory efforts executed via an appropriate business model. The contents of the current manuscript cover the essential elements of how companies have gone about creating and sustaining a successful DRPx company, as well as the associated business models that have been utilised.

Lessons from history

In a world cluttered only with thoughts of today and tomorrow, lessons from the past are usually forgotten. Even when the past is considered, it is often viewed through a 'success' distorted kaleidoscope. Pfizer successfully repurposed Sildenafil (Viagra) from angina to erectile dysfunction (1998), and subsequently to pulmonary arterial hypertension (PAH) in 2005. Celgene repositioned Thalidomide (Thalomid) from an anti-nausea medication to treatment of leprosy (1998) and multiple myeloma (2006). These stellar examples of success have fuelled an upsurge in the activity of DRPx and the creation of numerous new DRPx-focused start-up companies[1]. Novac has argued, however, that any analysis of DRPx companies that only considers 'success stories' obscures "the challenges that repositioned compounds have on the way to the clinic"[2]. Based on this thoughtful logic, we have analysed the history and fate of all DRPx-focused companies and DRPx-focused non-profit foundations. We have assembled a list based on the time period when each company/non-profit was formed. These data are summarised in **Table 1** and include the current operational status of each company/non-profit organisation. In our analysis we have only included companies/non-profits that provide specific DRPx services and platform technologies, as well as possess RRRDx candidate pipelines and marketed drugs. We have not included companies/non-profits that provide(d) a platform used predominantly in *de novo* DDD (eg KineMed) nor companies/non-profits that have a *de novo* DDD pipeline and only contains a single possible RRRDx candidate (Vanda Pharmaceuticals).

Systematic and sustained DRPx efforts are a relatively recent phenomenon. Perusal of **Table 1** reveals that this type of activity has only been undertaken in the past 20-25 years. During that time only a small number of companies have failed and ultimately ceased to exist. Such companies have either stopped trading or filed for bankruptcy. The actual cause of failure is sometimes difficult to ascertain. Often times a company simply ceases operations but fails to communicate the news to the market, as was the case with Cerimon Pharmaceuticals[3]. In other cases the cause is rea-

sonably well documented. It is noteworthy that in four cases a failed clinical trial(s) was the principal reason for the company's ultimate demise. For example AV-608 failed to exhibit significant clinical efficacy differences for the treatment of social anxiety disorder and led to Avera Pharmaceuticals shutting its doors in 2012[3]. Sention Inc could not produce enough compelling data for the use of L-Amphetamine in the treatment of cognitive impairment, as well as overcome the poor image of its lead candidate for a legitimate therapeutic use[4]. Sometimes the clinical trials failure led to a slow inexorable slide towards oblivion, but is only one part of the narrative. For example Gene Logic started corporate life (2001) as a successful genomics database and support services company, ultimately growing to ~450 employees. In 2007, however, it divested itself of the genomics service business, changed its name to Ore Pharmaceuticals and refocused its efforts on drug repositioning and development. After a series of unsuccessful clinical trials for its lead RRRDx candidates it became Ore Holdings in 2011, and ultimately ceased trading on February 12, 2015[5,6]. Similarly, the spectacular rise and fall of the DRPx giant CombinatoRx was due in part to a series of failed clinical trials. This is described in more detail in **Side panel I** in association with a condensed history of the company. Other noted causes of failure for DRPx companies include the inability to find appropriate commercial partners (eg Bionaut) or raise capital because of limited commercial prospects (eg Arachnova Therapeutics, Dynogen Pharmaceuticals and QuatRx Pharmaceuticals).

In the past, DRPx company efforts have been viewed as a primary source of rapid value creation and accretion. Even so, such companies have initially lacked significant capital and resources. Determined and focused DRPx efforts, however, within specialised niche disease areas, have ultimately led to acquisition by larger, more resource-rich companies. This exit strategy has usually been executed on within a 5-7 year period, with varying degrees of compensatory reward ranging from $25 million (Daniolabs) to $955 million (Aspreva Pharmaceuticals). Obviously such deals were determined by the depth and value of the individual DRPx company pipeline. For example, Aspreva was acquired by the Swiss drug wholesaler, Galenica Holdings in 2007 predicated in part on the FDA fast-track designation of a single RRRDx candidate, Mycophenolate (CellCept) for the new indication treatment of lupus nephritis[7]. In addition Aspreva had also concluded a deal with Roche that incurred royalties for the off-label use of the same drug in the new indication[2]. More recently, Actelion Ltd bought Ceptaris Therapeutics in 2013 for $250 Million for the gel formulated Mechlorethamine Hydrochloride (Valchor) used in the topical treatment of early stage mycosis fungoides-form cutaneous T-cell lymphoma[8]. By contrast Arakis had a robust, rich clinical pipeline consisting of AD-237 for the treatment of COPD, AD-452 for rheumatoid arthritis AD-923 for cancer pain, and five other candidates in clinical trials. They also possessed a

Side panel I: The rise and demise of CombinatoRx

CombinatoRx was a blazing star in the firmament of drug repurposing. The company was founded in 2000 by a group of Harvard/MIT scientists and entrepreneurs. They developed a proprietary platform technology to evaluate the synergistic activity of specific combination-pairs of approved drugs. A high throughput, cell-based screening assay platform was used in combination with a novel dose-matrix regime against a broad swath of major diseases including assorted cancers, rheumatoid arthritis, asthma, psoriasis and diabetes. Alexis Borisy (founding CEO) stated: "We wanted to explore how we could create platforms that would rapidly yield a portfolio of clinical product candidates. We took a very pragmatic approach of starting from known components: if you take a world of 2,000 known drugs, it gives you two million possible combinations. We created and patented the platform that allows us to systematically search for these novel combinations in multiple therapeutic areas[1]." This innovative drug repurposing initiative garnered significant investment and grant funding, IP and a vibrant early stage drug development pipeline, which led to a successful IPO (~$42 million) in November 2005. However, by 2010 the company was in trouble. It had burned through $230 million in funding and had encountered the brutal world of conventional drug development. It sought to reinvent itself with a name change to Zalicus and the hiring of a new CEO, Mark Corrigan. The slump in high flying performance had been caused in 2008 by the faltering of one of its lead candidates. Synavive failed to demonstrate any statistically significant benefits in a mid-stage clinical trial for the treatment of arthritis of the knee. In order to shore up its pipeline, CombinatoRx acquired the Canadian company NeuroMed Pharmaceuticals along with its opioid pain reliever, Exalgo. This single compound drug was subsequently approved by the FDA in April 2010. In addition it developed a new version of Synavive, but that failed to demonstrate improved efficacy in clinical trials when compared to marketed competitors and the company abandoned all developments efforts in September 2012. UK-based Horizon Discovery acquired the CombinatoRx/Zalicus service business and high throughput screening platform for $8 million in June 2014. Simultaneously, Zalicus announced a merger with Epirus, a Boston, US-based pharmaceutical company focused on rheumatoid arthritis, in a 10-for-1 reverse stock split. The demise of CombinatoRx/Zalicus was complete.

1 Interview –Alexis Borisy. Wall Street Transcript. (2003). http://www.twst.com/interview/15717.

Table 1: List of DRPx companies/non-profits grouped according to the year formed

COMPANY	FOUNDED	CURRENT STATUS[a]	NOTES/ACTIVE BUSINESS MODEL
A. Formed 1981-2005			
Avera Pharmaceuticals	2002	Defunct (2012)	Failed Clinical Trial
Arachnova Therapeutics	1998	Defunct (2008)	Asset Sale – Patent Portfolio Bought by Dynogen
Bionaut Pharmaceuticals	2000	Defunct (2005)	Inability to create Pharma Partnerships
Cerimon Pharmaceuticals	2004	Defunct (2011)	Executive Management Changes-No New Investment
CombinatoRx/Zalicus	2000	Defunct (2014)	Failed Clinical Trials
Dynogen Pharmaceuticals	2002	Defunct (2009) Filed for Bankruptcy	
Gene Logic/Ore Pharma	2001Defunct (2011)	Failed Clinical Trials	
QuatRx Pharmaceuticals	2000	Defunct (2013)	Assets Divested to Shionogi and Forendo Pharma
Sention Inc	1999	Defunct (2005)	Failed Trial on Lead Compound
Pharmos Corporation	1992	In Distress (2015)	No Website, Penny Stock
BioMedicines Inc	1995	Refocused (2004)	Changed Name – Intarcia & Focused Drug Delivery
BTG	1981	Refocused (2005)	Changed to Broad Range of Medical Products
Syntopix/Evocutis	2003	Refocused (2014)	Changed Name (2011) & Divested all Drug Assets
Arakis	2000	Acquired (2005)	Bought by Sosei – $187.5M
Aspreva Pharmaceuticals	2001	Acquired (2007)	Bought by Galenica – $915M
ChemgeneX Pharmaceuticals	2004	Acquired (2011)	Bought by Cephalon – $230M
Cypress Bioscience	1981	Acquired (2010)	Bought by PEG Ramius & Royalty Pharma – $255M
Daniolabs	2001	Acquired (2007)	Bought by VASTox – $25M
Hypnion	2000	Acquired (2007)	Bought by Lilly – $315M
Saegis Pharmaceuticals	1999	Acquired (2006)	Bought by Lundbeck A/S – $27M
Somaxon Pharmaceuticals	2003	Acquired (2012)	Bought by Pernix Therapeutic Holdings – $25M
Synosia Therapeutics	2005	Acquired (2011)	Bought by Biotie – $121.5M
Vela Pharmaceuticals	1998	Acquired (2006)	Bought by Pharmos – $29.7M
BM Systems	2004	Active	Pharma Services, Platform Technology
BioVista	1996	Active	Pharma Services & Drug Candidate Pipeline
Camargo Pharma	2003	Active	Consulting – Focus on FDA 505(B)(2) Process
Celentyx	2004	Active	Pharma Service & Drug Candidate Pipeline-Immune
CureHunter	2003	Active	Pharma Services & Drug Candidate Pipeline
Cures Within Reach	2005	Active	Non-Profit, Services, Facilitation, Education
Global Cures	2004	Active	Non-Profit, Patient Advocacy
GVK Bio	2001	Active	Pharma Services
HM Pharma Consultancy	2000	Active	Consulting & Pharma Services, IP & Regulatory
Melior	2005	Active	Pharma Services & Drug Candidate Pipeline
SEEK Group	2004	Active	Product Portfolio Management
Switch Biotech	1997	Active	Drug Candidate Pipeline – Dermatology
Sosei	1990	Active	Drug Candidate Pipeline & Approved Drugs

[a] The current status of the company is described and the (year) denotes time of business cessation, refocusing or acquisition
[b] OD – Orphan Diseases adapted, modified and updated after Novac[2]

further six pre-clinical candidates in development and two compounds in late-stage clinical research. Arakis was acquired by the Japanese DRPx company Sosei for $187.5 million in July, 2005[9].

At the other end of the value proposition spectrum, the Danish pharmaceutical company Lundbeck A/S acquired Saegis Pharmaceuticals and its lead compound SG-515 for $27 million. The compound had successfully traversed a USA-based Phase IIa clinical trial in 20 schizophrenia patients. However, Lundbeck subsequently conducted a full Phase II trial in Europe and Asia to further evaluate the compound (now known as Lu-AB58054) as an adjunct therapy to Risperidone, in the treatment of 124 schizophrenic patients. The results were never published but the developmental use of this compound for cognitive deficits in schizophrenia was discontinued. In yet another twist to the story, Lundbeck repositioned Lu-AB58054 (now known as Idalopirdine) again in 2010, this time for the treatment of mild to moderate Alzheimer's disease. It is currently being evaluated in four different Phase III clinical trials which are set to end in 2015-2016[10].

As noted above, corporate and non-profit DRPx-focused initiatives are relatively new. During the past 20-25 years, at least 67 DRPx-companies/non-profits have been created to the best of

Table 1 (continued): List of DRPx companies/non-profits grouped according to the year formed

COMPANY	FOUNDED	CURRENT STATUS[a]	NOTES/ACTIVE BUSINESS MODEL
B. Formed 2006-2010			
AviMed Pharmaceuticals	2009	Active	Drug Candidate Pipeline – CNS
CWHM	2010	Active	Non-Profit, Services & Platform-Neglected Diseases
EspeRare Foundation	2013	Active	Non-Profit, Services & Platform-Neglected Diseases
Marco Polo Pharmaceuticals	2008	Active	Drug Candidate Pipeline – CNS
nPharmakon	2008	Active	Pharma Services & Drug Candidate Pipeline
Pharnext	2007	Active	Drug Candidate Pipeline – Neurodegenerative
NovaLead Pharma	2010	Active	Drug Candidate Pipeline
Numedicus	2008	Active	Consulting & Pharma Services
Seachange Pharmaceuticals	2009	Active	Platform Technology – Computational Statistics
Serendex Pharmaceuticals	2008	Active	Drug Candidate Pipeline & Approved Drugs-Lungs
Sistemic	2010	Active	Platform Technology – Micro RNA
SOM Biotech	2009	Active	Drug Candidate Pipeline
THERAMetrics	2007	Active	Pharma Services & Drug Candidate Pipeline
TONIX Pharmaceuticals	2007	Active	Drug Candidate Pipeline – Focus CNS
Transparency Life Sciences	2010	Active	Drug Candidate Pipeline
Vivia Biotech	2007	Active	Drug Candidate Pipeline – Hematologic Cancers
Yaupon/Ceptaris	2002	Acquired (2013)	Bought by Actelion Ltd – $250M
C. Formed 2011-2015			
Anaxomics Biotech	2013	Active	Consulting & Pharma Services-Systems Biology
Epsilon 3	2014	Active	Consulting & Pharma Services
Kailash Biosciences	2014	Active	Compound Libraries
Intellimedix	2014	Active	Services & Precision Medicine Focus
NeXeption	2011	Active	Product Portfolio/Company Management
NuMedii	2011	Active	Platform Technology – Big Data
PharmaKure	2013	Active	Drug Candidate Pipeline – Focus Alzheimer's
Quantacea	2012	Active	Platform Technology – Quantum Modeling
Recursion Pharmaceuticals	2013	Active	Pharma Services & Drug Candidate Pipeline – OD[b]
ReDiscovery Life Sciences	2014	Active	Drug Candidate Pipeline
Re-Pharm	2011	Active	Pre-Clinical Candidate Pipeline
Revive Therapeutics	2012	Active	Drug Candidate Pipeline – Gout & OD[b]
Theranexus	2013	Active	Drug Candidate Pipeline – Psychotropic
WIPO Re:Search	2011	Active	Non-Profit Database & Services Neglected Disease

[a] The current status of the company is described and the (year) denotes time of business cessation, refocusing or acquisition
[b] OD – Orphan Diseases adapted, modified and updated after Novac[2]

our knowledge. In that timeframe, 11 companies (~16.5%) have been acquired for a total acquisition cost of $2.38 billion, 10 companies (~15%) have also failed and three companies (4.5%) have refocused their efforts away from DRPx. It is interesting to note that the failure rate of DRPx companies over a 10-year period is only ~29% (10 of 34 companies listed in **Table 1** formed on or before 2005). This is in contrast to the significantly higher failure rate of 40-50% in the general biotechnology sector[11,12]. Furthermore, there are currently 38 companies (~61%) still active and 25 of them (~66%) are focused on developing RRRDx pipelines and marketed drugs.

An historical analysis of the DRPx sector is revealing. Several salient issues emerge:

i The failure rate of companies in this sector is lower than general biotech. This may not be so surprising given the risk-minimisation strategies inherent in the DRPx process.
ii Failure appears to be due in some part to underfunding and limitation of resources.
iii A noticeable fraction of failed companies disappeared because of the hurdles imposed by conventional clinical trial issues.
iv The DRPx sector appears to be predominantly focused on producing robust clinical pipelines and market-driven therapeutic drugs.
v Overall the DRPx sector is vibrant and growing; with on average 14-16 new companies being formed every five years.
vi Exit strategies for DRPx companies by acquisition have been enormously successful.
vii DRPx companies have developed relatively successful strategies that interweave IP and regulatory

Side panel II: A different approach – Transparency Life Sciences

Transparency Life Sciences (TLS) is "the world's first drug development company based on open innovation". Founded in 2010, the company's initial project was to develop the repurposed drug Lisinopril as an adjunctive therapy in patients with multiple sclerosis. TLS's bold, encompassing vision is to reduce drug development costs by a minimum of 50% for its drug candidates by employing open data access, crowdsourcing and remote patient monitoring technologies. This innovative and daring effort is predicated on three defining principles, namely i) stakeholder participation in clinical trial design in the form of crowdsourcing; ii) leveraging recent advances in information and mobile health technologies to reduce patient site visits and enhance data quality while reducing costs; and iii) transparency through the clinical trials process to facilitate credibility with stakeholders such as patient participants.

It is instructive to consider the ongoing practical execution of its clinical trial design, which was approved by the FDA for the assessment of the repurposed use of Lisinopril. Initial funding of the trial was obtained by the successful submission and approval of a fast-track NIH/NCATS SBIR grant. Clinical trial design was completed with input from patients, physicians and TLS staff. IND approval was granted by the FDA for patients to only be seen at the start and completion of the Phase II trial. During the course of the trial patients did not have to leave their homes since they were being assessed using telemonitoring as part of the protocol. Dr Tomasz Sablinski (CEO & Co-Founder of TLS) has indicated that the approval process was relatively straightforward, and that the FDA appeared to be supportive of patient-centric study design. Furthermore he believes that "moving trials to patients rather than the other way round" and seeking their input on clinical trial design is the future of clinical trials

considerations in an attempt to gain market exclusivity for their products.

Value perception

The limitations of current pharmaceutical industry performance have been discussed extensively in the first article in this series[1]. The development and successful execution of well thought-through DRPx strategies can help alleviate such problems and add significant value to pharmaceutical company pipelines. In addition, such actions can also be of benefit to other stakeholders including clinicians/healthcare providers, payers, regulatory/government agencies and patients/consumers, the ultimate end-users of these products. At a macro level the specific issues that contribute to the value of DRPx include:

i Cost savings. Previously, Persidis has suggested that the cost "to relaunch a repositioned drug averages $8.4 million"[13]. This appears to a rather conservative estimation and may be more applicable to simple, line-extension DRPx cases. We estimate that the cost is closer to ~$300 million, assuming that the RRRDx candidate has to undergo Phase II and Phase III clinical trials. This is predicated on the model proposed by Paul et al[14], but still represents a ~85% saving, compared to the $1.778 billion cost of a *de novo* DDD drug. In addition, we believe that the choice of the DRPx technology deployed as well as innovative execution in the clinical trials stage can dramatically affect the final cost of the DDD process and is exemplified by the efforts of companies such as CureHunter (**Table 1**) and Transparency Life Sciences (see **Side panel II**).

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 RRRDx, again based on the model of Paul and co-workers[14]. We suggest this can be further reduced by innovation at the clinical trials stages predicated on the adroit use of companion diagnostics.

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)[14].

These poor success rates place tremendous pressure on the drug pipeline and hence pharmaceutical company productivity. Since RRRDxs 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 RRRDxs 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 RRRDxs moving from Phase III to market (only 50% for DDD drugs)[15]. In part this is due to the increased information content available for the RRRDx, thus enabling better, faster decisions to be made in terms of safety and efficacy. Optimisation of this data/information tethered to a specific candidate drug should only enhance the probability of success and decrease the risk associated with the clinical trial process.

iv Market potential. The market potential for a RRRDx is determined by the same market forces as a conventional DDD drug, and includes drug differentiation, market need, patient acceptance, marketing strategy and IP position[13]. Thus a RRRDx has the same possibility to achieve blockbuster status as a *de novo*-derived drug (see for example **Table 2** and discussions below).

Table 2: Top 10 mini-blockbuster and blockbuster RRRDxs

BRAND NAME	ORIGINAL INDICATION	NEW INDICATION (YEAR)	PHARMA COMPANY	ANNUAL SALES[a]
GEMZAR	Anti-viral	Various Cancers (Various)	Lilly	$1.72B
EVISTA	Osteoporosis	Invasive Breast Cancer (2007)	Lilly	$1.09B[b]
PROSCAR[c]	Hypertension	BPH (1992)	Merck	$741.4M
PROPECIA[c]	Hypertension	Male Pattern Baldness (1997)	Merck	$429.1M
REVLIMID	Structural Analogue[d]	Multiple Myeloma (2006)	Celgene	$4.28B
REVATIO[e]	Angina/ED	PA Hypertension (2005)	Pfizer	$525.0M
RITUXAN	Various Cancers	Rheumatoid Arthritis (2004)	Biogen/IDEC[f] & Roche	$1.2B[g]
TECFIDERA	Psoriasis	Multiple Sclerosis (2013)	Biogen/IDEC[f]	$2.91B
THALOMID	Anti-Nausea	Leprosy (1998)	Celgene	
		Multiple Myeloma (2006)	Celgene	$535.2M
VIAGRA[e]	Angina	Erectile Dysfunction (1998)	Pfizer	$2.05B

[a] Actually peak annual sales
[b] Peak annual sales includes both osteoporosis and breast cancer numbers
[c] Both brand names are the identical drug Finasteride
[d] This is a structural analogue of Thalomid – see text for discussion of why included
[e] Both brand names are the identical drug Sildenafil
[f] On March 23, 2015 Biogen/IDEC was renamed simply as Biogen

v Intellectual Property/regulatory strategy. 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[13]. In addition regulatory strategies can also facilitate market protection and in concert with IP protection can garner market exclusivity for the DRPx drug. This is discussed in more detail in the third manuscript in the series which will be published later this year[16].

vi Patient/health system. The advent of personalised/precision medicine has fuelled the transition of patients to consumers[17].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[18], as well as providing therapeutic efficacy where none existed previously, as with Sildenfil in the treatment of erectile dysfunction. In addition a RRRDx may show utility for a population subset that fails on the default standard treatment, has fewer side-effects for a given individual, or plays a powerful adjuvant role in a combination therapy with the primary agent. 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.

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. Another obvious challenge is that the efficacy of a RRRDx must be demonstrated. Clearly the RRRDx 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 RRRDx trial being abandoned. A final consideration of obstacles and hurdles that can confront the unwary is IP and regulatory issues. These can be complex and troublesome as a company attempts to navigate the DRPx process. Nevertheless, as noted above many of the current, practising DRPx companies have demonstrated successful tactical and strategic ways to overcome such obstacles (see **Table 1** for examples).

We and others have discussed and documented the numerous benefits of DRPx[1,13,18,19]. Nevertheless, there appears to be a perception that DRPx efforts contribute limited value to marketed drug pipelines. However, Persidis has estimated that DRPx drugs now generate $250 billion per annum, constituting ~25% of annual revenue, for the pharmaceutical industry[20]. In addition we have compiled a top 10 list of current mini-blockbuster (~$0.5 billion/year in sales) and blockbuster (>$1 billion/year in sales) RRRDxs and this is shown in **Table 2**. This analysis provides the trade name of the RRRDx, original and new indication(s) as well as peak annual sales (PAS)[21]. The most widely-cited DRPx success examples are Viagra (Sildenafil) and Thalomid (Thalidomide). Therefore it is not unexpected to find them both listed in **Table 2** with a PAS of $2.05 billion and $535.2 million respectively. It is also interesting to note that Sildenafil was subsequently repositioned again in 2005 as a treatment for PAH with a PAS of $525.0 million. In order to avoid confusion with Viagra, Sildenafil was rebranded as Revatio for this new indication. In the case of Thalomid, Celgene also received approval by the US FDA (2006) for Revlimid (Lenalidomide) to be used in combination with dexamethasone to treat patients with multiple myeloma. This drug is not strictly a repurposed drug but is a structural analogue of Thalidomide. However, it is part of the RRRDx family of Thalomid, even possessing the same teratogenic effects, and is thus included in the top 10 list (**Table 2**).

A more recent example of a RRRDx blockbuster is Tecfidera (Dimethyl Fumerate) marketed by Biogen IDEC. It was approved for a new indication to treat multiple sclerosis (MS) in 2013, and achieved stunning revenue sales of >$2.91 billion worldwide in 2014. This represented ~30% of total revenues for Biogen/IDEC last year. Tecfidera is one of three recently approved drugs for the treatment of MS. The other two *de novo* derived drugs are Gilenya (Fingolamide) developed by Novartis and FDA approved in 2010, and Aubagio (Teriflunomide) from Sanofi-Aventis and approved by the FDA in 2012. The DRPx drug Tecfidera was priced at ~$55,000/year, whereas Gilenya is more expensive at ~$60,000/year, and Aubagio is cheaper at ~$48,000/year. It is noteworthy that Tecfidera is outperforming the other two drugs predicated on

its safety and efficacy profiles. Analysts are predicting that Tecfidera will dominate the market share of oral MS therapies and estimate annual sales reaching ~$3.5 billion by 2017[22]. Biogen/Idec has rights to another blockbuster RRRDx on the top 10 list, namely Rituxan (Rituximab). This chimeric antibody was originally developed by IDEC and received FDA approval in 1997 for the treatment of non-Hodgkin's lymphoma. It was subsequently repurposed for rheumatoid arthritis (RA) in 2004. The RRRDx drug is marketed in the USA by Biogen/Idec and Genentech, and by Roche in Canada and Europe. The PAS of Rituxan for RA is $1.2 billion, and the total PAS for assorted cancers and RA is $3.46 billion[23]. Finally, Evista (Raloxifene) is a drug used in the treatment of osteoporosis in postmenopausal women. In 2007 it was repurposed as a treatment for invasive breast cancer in women with osteoporosis. Based on these latter findings both the FDA and EMEA granted orphan drug status for Evista, thereby guaranteeing seven years more of market exclusivity "for cost recovery reasons"[24]. The PAS of $1.09 billion noted in **Table 2** is reflective of both osteoporosis and breast cancer treatment sales.

Stakeholders and value

Historically, the pharmaceutical industry has tightly controlled the DDD process pipeline, drug launch, marketing and post-marketing surveillance of its therapeutic drug products. Hence by association large pharma exerts considerable influence in the DRPx sector and to some extent on DRPx-focused companies. As discussed previously, however, a changing landscape of other influential stakeholders now exists[1]. These stakeholders now bring to bear a set of demands that the pharmaceutical industry must take into consideration as the latter grapples with the perceived need and value of RRRDx products. The various stakeholders, including the pharmaceutical industry and their roles/influence on DRPx companies and initiatives are discussed below.

i. Pharmaceutical companies. According to a number of reports, DRPx constitutes anywhere from 10-50% of current R&D spending, and is a determinant factor in the lifecycle management of pharmaceutical products[2]. Most of the larger pharmaceutical companies have embraced 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)[25]. In contrast companies such as Roche, Celgene and Allergen perceive candidate compounds from a polypharmacological perspective and therefore a potential treatment for multiple diseases[15]. Other large pharma companies that have dedicated internal resources specifically to DRPx include Novartis (New Indications Discovery Unit), Bayer Healthcare Pharmaceuticals (Common Mechanism Research group) and Glaxo Smith Kline (Systematic Drug Repositioning Group. 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. Pfizer, in addition to AbbieVie, AstraZeneca, Bristol Myers Squibb, Lilly, GlaxoSmithKline, Sanofi-Aventis and Janssen has collectively made a number of its abandoned compounds available for DRPx. A similar initiative was announced by Astra Zeneca with the Medical Research Council (MRC) in the UK. All this activity appears to indicate recognition on the part of pharmaceutical companies that there is value in rescuing and recovering shelved and/or abandoned compounds but with limited uptake of risk and investment on their part.

ii Generic pharmaceutical companies. Historically, generic drug companies have operated in a market determined by price and distribution channel metrics. In contrast pharmaceutical companies have relied on IP and regulatory protection strategies to drive market exclusivity. Today both generic and pharmaceutical companies are often times in direct competition as they enter a single healthcare market sector. Thus, when Teva Pharmaceutical Industries Ltd announced the creation of its 'New Therapeutic Entity' initiative (2013) for DRPx, it created a stir in both the pharmaceutical and DRPx communities[26]. Teva is the world's largest generic drug manufacturer and was also ranked as the 11th largest 'pharmaceutical company' based on its revenue numbers for 2014[27]. The publicly-announced decision to focus some of its resources on DRPx was designed to acquire products that were "innovative enough to justify high price tags and well recognised by regulators so as not to require arduous clinical trials"[26]. In that regard Persidis has argued that generic drug development and drug repurposing are "highly synergistic"[28]. DRPx obviously facilitates new formulation, delivery, dosing and indications that open up new markets and revenue streams. In addition the relative speed of developing a repositioned drug plays well to the shortened development timescales of the generics industry. This nascent activity by Teva indicates that the generic pharmaceutical companies will continue to pay close attention to DRPx

Side panel III: The mouse model of success at Melior

Dr Andrew Reaume, CEO and Co-founder of Melior Discovery, walked the halls of Pfizer when quaint notions such as 'target validation' and 'knock-out mice' were the tools of the trade in the DDD world. This was during the time that the Human Genome Project was completed, and led to a stampede of grandiose new ideas to ostensibly improve the DDD process. However, Dr Reaume persevered with an idea he conceived at Pfizer to utilise changes in the phenotype of a series of genetically-modified mice as disease models when challenged with a therapeutic agent. He left Pfizer in 2005 and co-founded Melior Discovery in order to implement this simple but powerful strategy as well as develop the platform. Once initial seed monies were raised, he re-engaged with Pfizer and convinced it to become an alliance partner in this new endeavour. Melior Discovery's phenotypic screening platform consists of approximately 40 different 'gold-standard' animal models covering 14 major and broad therapeutic areas. Over time it has industrialised this process by multiplexing animal model experiments. The result is its signature theraTRACE platform used to find new drug indications. It suggests that such an approach, which is not hypothesis driven, leads to an unbiased analysis which can result in "unexpected" results and insights in drug repositioning studies. At present ~80% of the company's efforts are providing DDD services to a number of pharma clients, focused primarily in drug repurposing/repositioning/rescue. In addition it invests ~20% of its energy into R&D. In the latter case this has led to some exciting developments and a pipeline of repositioned drugs with new indications. For example, just this year Melior started a FDA-approved Phase II clinical trial for one of its lead repositioned drugs (MLR-1023) in 120 Type II diabetic/control patients. MLR-1023 is an oral insulin sensitiser, which improves glycemic control by selectively activating the Lyn tyrosine kinase enzyme. It has two other repositioned drug candidates in its pipeline, namely MLR-1017 and MLR-1130 for the treatment of Parkinson's disease and dermatitis respectively. Each compound is spun out into a separate subsidiary company, Melior Pharmaceuticals. This simple but elegant business model allows for development of specific therapeutic areas of focus, as well as facile management control and a potential clean exit strategy. Most of Melior Discovery/Pharmaceuticals competitors employ some type of computational biology discovery platform for generation of its repurposed candidate drugs. However, Melior has taken an approach that is steeped in pharma tradition but has proved to be extremely effective.

efforts and explore suitable avenues for exploitation in keeping with their current business models.

iii Contract Research Organisations (CRO). Their primary focus is offering a wide range of services to the pharmaceutical industry. Based on such a conservative business model, RRRDxs and services afford limited value to CRO companies. Indeed arguments have been made that any activity in this arena may be construed as competing directly with their pharmaceutical company clients. More recently it has been suggested that CROs proactively engage in developing discovery and DRPx capabilities as a component of their full service portfolios. CROs that support and integrate these capabilities are then in a position to offer major pharma clients turnkey solutions that feed discovery data into fast track FDA liaison, trial recruitment and forward-looking channel development solutions. CureHunter Inc is one DRPx company that has emphasised this turnkey partnership approach. Moreover, some of the more aggressively inclined CRO companies such as Quintiles, WuXi PharmaTech and Evotec have announced that they will invest directly in drug discovery and development projects[29]. Obviously the lines between the pharmaceutical and the CRO sectors are being blurred and the impact of such a transition on the DRPx sector is somewhat unclear at the moment.

iv Clinician/healthcare provider. The availability, safety and efficacy of any therapeutic drug are of critical value to the clinician as they look to optimise treatment and specific disease management of their patients. The activity of numerous DRPx companies and non-profits in orphan and neglected disease areas offers the potential of new relatively fast and cheap treatments for hitherto ignored or under-served diseases. Such product

offerings would presumably be well received by the clinical and healthcare provider communities. Ironically, the ability of clinicians to write off-label prescriptions for disease treatments has led to unintended, but nonetheless real concerns about the value of DRPx drugs for new indications due to exclusivity issues and this is discussed more in our third paper of the series[16].

v Patient/consumer. The advent of personalised medicine and the transition of patients to consumers have resulted in a more demanding customer base[17,30]. As in any other industry sector, and noted above the customer is primarily interested in a faster, cheaper, safer, more effective products. In this regard the offerings of RRRDxs are very much in keeping with the demands of the consumer/patient. In addition under-served patient populations are being provided for by the significant DRPx activity in orphan and neglected disease areas. However, all these positive elements of overlap are not being translated into vocal support for the DRPx industry. In part this is due to the fact the cost/price of a drug is important to the consumer only in the context of the reimbursement process. Thus, patients/consumers are for the most part blissfully unaware of DRPx activities and the potential impact on them as either an individual or as part of a population.

vi Payer. The cost/price of the drug is of primary importance to the payer. In addition they are looking for the most cost-effective treatment, and increasingly are using comparative effectiveness analyses to make determination of which drug should be used. In some regards payers view DRPx drugs in a similar light as they do generic drugs. But given the general perception that drugs are individually too expensive and that ageing populations of patients are frequently taking numerous discrete agents simultaneously, it is possible that high volume manufacturers with deep RRRDx pipelines derived from existing generics – even without unique IP protection – will become highly profitable based on volume rather than price.

vii Regulatory agencies. The performance characteristics of the drug are obviously the primary focus of the regulatory agencies. Agencies have developed guideline and approval processes for RRRDxs. However, as noted in **Side panel II** the regulatory agencies, such as the FDA, look favourably on innovative clinical trial design. This is one area where the DRPx industry needs to evaluate its contributions and follow the lead of innovators such as Transparency Life Sciences (see **Side panel II**).

All the different stakeholders perceive different value propositions of a RRRDx. In some cases those interests may be radically divergent, as in the case of the cost/price of the RRRDx. The DRPx developer/manufacturer would prefer to realise a high margin on the price charged to the end user, the customer, whereas the payer would obviously prefer to reimburse at a limited rate. Clearly, the value to the patient who needs treatment for his/her orphan or neglected disease is of paramount importance but could ill-afford a costly drug serving the needs of a limited population. This is in stark contrast to the DRPx/pharmaceutical company that has expended considerable financial assets to produce a clinically relevant drug and is looking to recoup those sunken costs and build a successful business. To further compound matters, the pharmaceutical companies continue to display a wariness of the DRPx sector as they are unsure about the true value of RRRDx because of perceived weaknesses in IP and regulatory strategies. However, in all cases it is imperative that lines of communication are developed in order to ensure the successful development and acceptance of high-quality RRRDxs continues into the future.

DRPx business models

Substantial growth in the DRPx sector has resulted in the emergence of a number of dedicated DRPx companies and non-profits organisations. These entities cover the gamut of capabilities and offer everything from consulting services, education, and facilitation to marketed drug products. Many of the companies 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 RRRDx pipeline. This assortment of companies/non-profits has led to the adoption of a number of different DRPx business models (see **Table 1**) and are described and discussed below.

i Consulting. There are five companies that offer specialised consulting services on a broad range of subject matter. For example Camargo Pharma offers detailed advice and insight on the FDA 505(B)(2) process used in the NDA approval protocol for RRRDxs. In contrast, HM Pharma Consultancy provides a broad range of service offerings to pharmaceutical and DRPx companies involving strategy, IP and regulatory issues. All these companies offer a standard fee-for-service business model.

ii Pharma services and platform technology services. Currently there are eight companies that offer

Side panel IV: A non-profit but NOT non-productive – Cures Within Reach

Dr Bruce Bloom has had a rich, varied and illustrious career. He was/is a dentist (DDS-University of Illinois-Chicago), an attorney (JD-Illinois Institute of Technology), entrepreneur (owner/operator of a fast food restaurant), and entertainer/educator (radio talk show host on ReachMD). A common thread interweaves through all these endeavours that includes the creation of innovative business opportunities and helping other people. This theme continued when he became the Executive Director of the Goldman Philanthropic Partnerships in 2002. Subsequently, he became the founding President of Partnership for Cures (2005), which changed its name to Cures Within Reach (CWR) in 2012 to better reflect the mission focus of "repurposing drugs and other treatments to speed cures to patients". CWR is a non-profit 501(c)(3) organisation that utilises drug repurposing as a vehicle to expeditiously deliver safe and cost-effective therapeutic treatments to patients in areas of unmet need that encompasses rare, neglected or common diseases. Their primary mission is threefold in nature and attempts to provide i) new treatments/cures for patients; ii) education about drug and device repurposing and iii) facilitation of the drug and device repurposing process. These efforts have been remarkably successful. At present 12 repurposed drugs or devices are either in clinical trials or actually used by patients, due to in no small part to the support and initiative of CWR. As an example, consider the orphan disease autoimmune lymphoproliferative syndrome (ALPS), This once untreatable disease causes anaemia and increased infection rates in children, and patients rarely lived beyond their 20s. CWR helped to provide funds for Dr David Teachey (Childrens Hospital of Philadelphia) to investigate the repurposed, new use of Rapamycin (Sirolimus). The efficacy studies and clinical trials took less than 36 months and the drug was approved for the treatment of ALPS. The consequence of these efforts is that Rapamycin-treated ALPS children no longer have to spend 5-10 days per month in hospital, and the medical bills for such patients were reduced by more than $100,000 per year. Another example of the early stage funding impact of CWR is the well-known repurposing of thalidomide for the treatment of multiple myeloma (MM). CWR-funded work at the Mayo Clinic by Dr S. Vincent Rajkumar led to one of the first evaluations of thalidomide treatment for MM. Such early seeds ultimately resulted in the development and approval of the Celgene drug Revlimid (a thalidomide analogue), now a blockbuster repurposed drug. Today CWR continues its work and outreach programmes. Currently it is engaged in discussions with the UK Government about the economic aspects of drug repurposing. The work does not stop and its impact and productivity in drug repurposing as it impacts patients continues unabated.

DRPx platform technology service capabilities to the pharmaceutical industry. These platforms are primarily utilised in DRPx discovery mode. They offer a wide-range of capabilities and include approaches that utilise systems biology (BM Systems), quantum modelling (Quantacea), big data manipulation (Numedii), precision medicine (Intellimedix) and computational statistics (Seachange Pharmaceuticals). These companies offer a fee-for-service business model, or in some cases, such as Seachange, provide an actual product (SEAware prediction software). In the case of the platform services companies they are vying for pharmaceutical contracts on a fee-for-service basis. However, one of the difficulties for each of these companies is the ability to differentiate their individual platform from others to the potential pharmaceutical client. The one exception to the platform technology services model is Kailash Biosciences. It currently offers "480 Smart-Compounds drugs which have regulatory approval for human use and have been selected for their diverse pharmacological properties and their scarcity". Compounds are offered for sale either in a 96-well plate (60 compounds per well) or individual vial format.

iii Pharma services and drug candidate pipeline: There are currently seven companies that operate a hybrid pharma services/RRRDx pipeline business model. BioVista is one such company and is widely

regarded as a pioneer of dedicated DRPx efforts. It provides a variety of service offerings to the pharmaceutical industry but also has a DRPx discovery platform that has been utilised to create a RRRDx pipeline with candidate compounds for a variety of disease indications.

CureHunter has taken a slightly broader approach in the implementation of this hybrid business model. The purpose built automated, computational linguistics/systems biology/Artificial Intelligence platform provides an information output that is molecular target neutral, in that any known small molecule, biologic, drug candidate or drug efficacy/safety factor can be determined for any therapeutic intervention for any disease. Such an approach can be used in both DRPx and *de novo* discovery and development. In addition the company produces a full suite of clinical decision support solutions for patients, physicians and payer-providers of health care services. Physician direct web access to the extensive clinical databases enables evidence-based, patient outcome-centric selection of optimal medications for the treatment of human disease in real time at the point of care and the mapping of biomarkers/diagnostics/companion diagnostics to the Electronic Health Record. This more expansive service approach model has afforded a multi-source revenue stream. The drug pipeline generated from the platform is unique in that it comprehends a molecule to medicine pathway that is directly back propagated from the outcome-centric efficacy and safety data developed for the clinical decision support analytical services. The close coupling of known drug outcomes to molecular structures from treatments of more than a billion patients in the core CureHunter database increases the predictive accuracy of the new drug discovery and repurposing algorithms substantially while reducing unexpected safety and toxicity potentials that can often occur late at very expensive points in the development cycle. This has led to a number of drugs being repurposed and prescribed off-label by physicians for individual patients as well as the creation of an in-house pipeline across a number of areas including oncology and autoimmune diseases. Also each individual drug candidate in the pipeline is correlated specifically with associated safety, toxicity, biomarker and companion diagnostic information that can support proof of principle for new indications and further reduce the risk of failure in the clinical trials process.

Melior Discovery has also taken this hybrid business model approach to DRPx utilising *in vivo* animal models to determine safety and efficacy of potential drug candidates. The operational aspects and business model of Melior Discovery are discussed in much more detail in **Side panel III**. All these companies utilise their service revenues to fund the operations of the company as well as enable DRPx discovery and development. The exit strategy involving compounds in the RRRDx pipeline is to either out-license, partner and/or have the compound(s) acquired at a suitable point during the development process in order to move the RRRDx to market.

iv Candidate drug pipeline. Most of these 14 companies are developing a business model predicated on out-licensing, selling or partnering at an early development stage in order to capitalise on the candidate drug value as well as facilitate its progress to market. In addition nine of the companies have elected to focus on specific disease-area franchises that include CNS (3), neurodegenerative diseases (2), dermatology (1), hematological oncology (1), gout (1) and psychotropic disorders (1). For example, Switch Biotech has RRRDx candidates in preclinical and Phase I trials for psoriasis, vitiligo and atopic dermatitis and is looking for opportunities to out-license and/or partner. On the other hand Vivia Biotech specialises in hematological cancers and has partnered with a Spanish pharmaceutical company in order to take its lead candidate V-009 through development and to market for the treatment of non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Five other companies are developing pipelines predicated on opportunity exploration and thus have RRRDx candidates across a multitude of disease areas. For example, Rediscovery Life Sciences has a RRRDx lead candidate, RLS-003, ready to enter Phase II trials for the treatment of acute kidney injury, but also has pipeline candidates for indications in Alzheimer's disease, wound healing, assorted cancers, lupus nephritis, peripheral artery disease and autism spectrum disorder. In a similar vein, SOM Biotech's model is to provide "intellectual protection, clinical validation and licensing of already available drugs for their development and commercial use in unknown indications". The lead compound SOM-226 is in Phase II clinical trials for the treatment of transthyretin-hereditary amyloidodsis. It also has drug candidates for Huntington's, benign prostatic hyperplasia, amnesia, Alzheimer's and Glioblastoma.

Several companies are exploring a business model that is somewhat more high risk, but with potential higher reward in terms of taking a drug through development and to market. For example, Pharnext's approach consists in "building a proprietary network of biological perturbations associat-

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ed with each disease based on extensive human genomics. This network is then used to deduce synergistic combinations of drugs already approved in other indications that can target multiple disease-related pathways". It refers to these combinations as "pleodrugs", and the approach and model are reminiscent of CombinatorRx/Zalicus (see **Side panel I**). Based on this pathway it has developed a small but promising pipeline for potential treatments of the Orphan disease Charcot-Marie-Tooth disease (adult and children), Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis (ALS). The lead candidate PXT-303 has just entered Phase III trials for adult Charcot-Marie-Tooth disease in adults and is funded in part by the company and the Hereditary Neuropathic Foundation. In contrast Transparency Life Sciences is taking a new, as yet unproven, approach to DRPx discovery and development. It sources its RRRDx candidates "from the hundreds of distressed clinical-stage compounds that have potential for rescue or repositioning". The company and its business model is discussed in more detail in **Side panel II.**

v Marketed drugs. Four companies have marketed RRRDxs as part of their product portfolios. A variety of business model approaches have been utilised to achieve such goals. Sosei is a global pharmaceutical company based in Japan and formed in 1990. The company developed its proprietary Drug Reprofiling Platform in 1999, and embarked on an ambitious and aggressive foray into DRPx[31]. As discussed above and noted in **Table 1**, it acquired the RRRDx candidate-rich company Arakis in 2005[9]. The strategy for filling their pipeline is predicated on a 'risk-controlled' model. It searches globally for RRRDx candidates with a "reduced risk, time and cost" required for development. High-risk, early-stage discovery and development candidates are not part of Sosei's current development strategy. In order to gain access to DRPx candidates it either acquires companies, such as Arakis, or in-license compounds. In the latter case it has in-licensed Norlevo (Levonorgestrel), an emergency contraceptive pill from HRA Pharma; Seebri (Glycopyrronium Bromide) a treatment for COPD from Novartis; and Ultribro (combination therapy of Glycopyrronium Bromide and Indacaterol) also for the treatment of Chronic Obstructive Pulmonary Disease from Novartis.

A very different business model is employed by the biopharmaceutical management company NeXeption. The parent company acquires a drug candidate that has considerable biological, toxicological and possible target/MOA information associated with the compound, ie a good candidate for repurposing. An independent corporate entity is then created around the compound in order to fund clinical trials and maximise the value of this asset. The NeXeption management team led by CEO Steve Tullman vets and selects candidate drugs then develops, registers and facilitates commercialisation of the new product. The preferred exit strategy of the NeXeption team is acquisition of the candidate drug (or marketed drug) and the 'housing company'. Tullman has argued that "licensing his companies' products is not a preferable option because such agreements require the licensee to pay corporate taxes on the value of the deal and pay dividends to investors, who are hit with income tax... I have each asset in its own vehicle... This is all about having separate assets and letting them blossom individually"[32]. A recent example of the successful execution of this model was the acquisition of Ceptaris by the Swiss company Actelion Ltd in 2013 (**Table 1**). Actelion paid $25 million up front but the deal was contingent on the candidate drug receiving FDA approval, at which point a further payment of $225 million was made. In addition Ceptaris shareholders were entitled to backend payments based on sales and other commercial milestones of the drug[8]. Ceptaris (originally known as Yaupon Therapeutics) had successfully repurposed the nitrogen mustard Mechlorethamine (Valchor) as a topic gel for the treatment of early stage mycosis-fungoides-type cutaneous T-cell lymphoma, which the FDA approved for use in 2013. NeXeption currently has two other 'house companies' in its portfolio, namely Aclaris Therapeutics and Alexar Therapeutics.

A similar business model is used by the London-based SEEK Group. The holding company develops its product portfolio in a variety of ways that mostly involve drug repurposing efforts. It has a diversified pipeline portfolio. However, SEEK differs from NeXeption in that it assembles a suite of products of a similar nature and then bundles them into a separate corporate entity. For example, one of its portfolio companies is infirst HEALTHCARE. This company has a range of RRRDx products focused on "innovative treatments" for coughs, colds and inflammatory pain. In a similar vein, Augement Oncology is using a RRRDx combi-therapy approach to develop treatments for an assortment of cancers with lead candidates in prostate, lung and breast cancer.

Finally, the Danish DRPx company Serendex, has a pipeline of candidate drugs and drugs repurposed for treatment of a number of severe lung diseases.

Serendex is a boutique DRPx pharma company, with a conventional pharma-like business model.

vi Non-profits. Corporations are pursuing DRPx efforts for a multitude of reasons but are primarily driven by the need to generate revenues. However, non-profits are focused on serving other needs be it orphan and/or neglected diseases or where there is other unmet patient need. For example, 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 accesses compounds from a variety of sources to evaluate in their pre-clinical models. Currently it has ongoing DRPx projects in childhood diarrhoea, tuberculosis, malaria, sickle cell disease and a number of rare diseases such as idiopathic pulmonary fibrosis. However, the primary focus of the non-profits is to ultimately serve the needs of individual patients and population groups. This is typified by the work of Cures Within Reach and this is described in more detail in **Side panel IV**.

DRPx pharma business models

Currently there is no single, widely-adopted business model applied by the pharmaceutical industry to drug repurposing. It is instructive to consider why that is the case. Novac has argued that DRPx success stories emanating from pharmaceutical companies have "drastically declined in recent years"[2]. It further suggests that successful RRRDx examples (eg Sildenafil and Thalomid) occurred before the advent of systematic discovery efforts, and were a result of "serendipitous discovery". It is possible that the entrenched, silo-structured, pharmaceutical companies are not conducive corporate structures for DRPx. They are organised typically by specific disease areas and new indications for a RRRDx may often times fall outside these areas of clinical focus and specialisation. In addition there appears to be a sentiment that DRPx is not an endeavour that produces innovative research and outcomes. Finally, any new project including DRPx efforts requires investment, and as the candidate drug has often times 'failed' previously then there is a reticence to invest further in such an asset.

At present there appears to be three different DRPx pharmaceutical models:

i In-house. Some pharmaceutical companies have dedicated internal resources specifically to DRPx and they include Novartis, Bayer Healthcare Pharmaceuticals and GlaxoSmithKline. However, so far this model has had limited success and Pfizer abandoned this approach in 2013 when it closed the doors on its Indications Discovery Unit.

ii Out-licensing. Pharmaceutical companies have demonstrated a new willingness to provide access to their compounds on an out-licensing basis. This is typified in the recently announced formal MRC/Astra Zeneca collaboration as well as the NCATS initiative in the USA. In addition a number of pharmaceutical companies are receptive to direct approach by individual biotech companies to license compounds. As noted above, this is a relatively easy model for pharmaceutical companies to adopt since they are limiting any exposure to risk and additional costs for that compound.

iii Extended profiling. A drug candidate, after a successful first-in-human study is immediately evaluated in promising new indications. Novac has argued that "extending compound profile early on gives developers an opportunity to learn not only about the efficacy in alternative indications but also about the potential side-effects associated with certain co-morbidities thereby derisking the pipeline"[2]. In addition this model is much more cost-efficient than conventional models. This model has been adopted by a number of pharmaceutical companies and was pioneered by Roche[15]. More recently companies such as Celgene and Allergen have found considerable success using this approach. For example an examination of Celgene's recent 2014 annual report reveals that Otezla (Apremilast), its approved psoriatic arthritis drug, is also approved for psoriasis, is in Phase II trials for atopic dermatitis and ulcerative colitis, and in Phase III trials for ankylosing spondylitis. This multi-pronged DRPx approach is used by Celgene in all of its candidate drugs and approved drugs[33].

Conclusions

The mantra is the 'pharmaceutical industry is struggling with rising costs, cycle times and risk associated with the DDD process'. DRPx appears to offer some real solutions to these problems. The DRPx sector is vibrant and growing year-on-year. It has a relatively low company failure rate. The sector is diversified in terms of business models. RRRDxs contribute ~25% of annual revenue rates to the pharmaceutical industry. The top 10 mini-blockbusters and blockbusters have produced a total of ~$12.89 billion in PAS. What's not to like?

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