# Therapeutic Drug Repurposing, Repositioning and Rescue

## *Part IV: Financial model and analysis*

**By David M. Kauppi and Dr Stephen Naylor**

There is a growing consensus that Drug Repurposing, Repositioning and Rescue (DRPx) impacts all stakeholders involved in the therapeutic drug sector. In part, this is due to the fact that the pharmaceutical industry accrues ~25% of its annual revenue from DRPx products. However, a number of misperceptions are associated with this sector, and that has led to limited growth and development. Historically, many of the smaller, DRPx-focused companies have relied on large pharmaceutical entities as their primary source of revenue. This has usually been in the form of a fee-for-service, or technology platform/product licensing model. The problem with such business models is that large pharmaceutical companies have been, and continue to be, ambivalent towards externally-sourced DRPx endeavours. In order for individual DRPx companies to be successful, they must rely less on large pharmaceutical companies and focus more on building their own unique product pipeline in the form of repurposed, repositioned and rescued drugs. They must provide a compelling narrative about the enhanced value proposition of DRPx products compared to *de novo*-derived therapeutic drugs. This is necessary to raise the significant start-up and growth capital required to carry out such activities. In this final paper we discuss the issues of risk, time, cost and value enhancement associated with bringing a DRPx derived drug to market. In addition we present a comparative financial analysis of a *de novo*-derived drug versus a DRPx-derived drug on reaching the market, using Net Present Value (NPV) and Internal Rate of Return (IRR) considerations.

In the past year we have published a series of articles on Drug Repurposing, Repositioning and Rescue (DRPx)[1-3]. We noted that DRPx emerged in the early 1990s, and that all these interchangeable descriptors of DRPx usually refer to the process of identifying new indications for existing drugs, abandoned or shelved compounds and candidates under development[1]. It has also been proposed that Drug Repurposing should be used as a ubiquitous term that includes 'all the redevelopment strategies based on the same chemical structure of the therapeutically active ingredient as in the original product'[4]. Mucke has suggested 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"[5]. Drug Repositioning is defined more specifically, as the process of finding a new indication for an approved drug[5]. Finally, Drug Rescue refers to the development of new uses for chemical and biological entities that previously 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[5].

Much of the impetus for DRPx development has come ostensibly from specific non-profit and small biotechnology companies. In the past 20-25 years ~70 non-profit organisations and companies have been created that are dedicated to DRPx efforts[2]. During that same timeframe, 11 companies have been acquired for a total of $2.38 billion, 10 companies have failed and three companies 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 ~30%[2]. This is in contrast to the significantly higher failure rate of 40-50% in the general biotechnology sector[6]. Overall the DRPx sector is vibrant and growing; with an average ~15 new companies being formed every five years. Furthermore, at least 25 of the current ~40 DRPx active companies are focused on developing drug candidate pipelines and producing marketable drug products[2].

The advantages that accrue from DRPx efforts are compelling when the market potential of a repurposed/repositioned/rescued drug (RRRDx) is considered. Such RRRDx price points are determined by the same market forces as for a *de novo*-derived Drug Discovery and Development (DDD) product, and include drug safety and efficacy differentiation, market need, patient acceptance, marketing strategy and IP position. Thus a RRRDx has the same possibility to achieve blockbuster status as a *de novo*-derived drug. We have highlighted this phenomenon by listing a 'top 10' of current mini-blockbuster (~$0.5 billion/year in sales) and blockbuster (>$1 billion/year in sales) RRRDxs[2]. This compendium of drugs includes Evista, Gemzar, Proscar, Propecia, Revlimid, Revatio, Rituxan, Tecfidera, Thalomid and Viagra. It is noteworthy that all the drugs listed were developed and are sold by large pharma or large biotechnology companies. The top 10 mini-blockbusters and blockbusters have produced a total of ~$12.89 billion in peak annual sales alone. Based on such compelling revenues, it is not surprising to learn that DRPx constitutes anywhere from 10-50% of current pharma R&D spending[2]. DRPx efforts are a determining factor in the lifecycle management of pharmaceutical products, and Persidis has estimated that RRRDx products generate ~25% of total annual revenue for the pharmaceutical sector[7].

Many of the larger pharmaceutical companies continue to embrace in-house DRPx efforts via a formal or *ad hoc* mechanism. One notable exception appears to be Merck, which remains cautious because of its experience with the NSAID, Rofecoxib (brand name Vioxx)[1]. In contrast companies such as Roche, Celgene and Allergen evaluate drug candidate compounds from a polypharmacological perspective and therefore consider each one as a potential treatment for multiple disease indications[2]. Other large pharma companies that have dedicated in-house resources to DRPx include Novartis (New Indications Discovery Unit), Bayer Healthcare Pharmaceuticals (Common Mechanism Research group) and TEVA, which 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. In this latter programme, eight pharmaceutical companies (AbbieVie, AstraZeneca, Bristol Myers Squibb, Lilly, GlaxoSmithKline, Sanofi-Aventis, Janssen and Pfizer) have collectively made 58 of their shelved or abandoned 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 year, and allows unprecedented access to AstraZeneca's compound library[2,3].

Substantial growth in the DRPx sector has resulted in a myriad of capabilities provided by specific

## References

1 Naylor, S and Schonfeld, JM. Therapeutic Drug Repurposing, Repositioning and Rescue: Part I-Overview. Drug Discov. World Winter Edition. 54-62 (2015).

2 Naylor, S, Kauppi, D and Schonfeld, JM. Therapeutic Drug Repurposing, Repositioning, and Rescue: Part II- Business Review. Drug Discov. World Spring Edition. 57-72 (2015).

3 Naylor, S, Kauppi, D and Schonfeld, JM. Therapeutic Drug Repurposing, Repositioning, and Rescue: Part III- Market Exclusivity Using Intellectual Property and Regulatory Pathways. Drug Discov. World Summer Edition. 62-69 (2015).

4 Murteira, S, Ghezaiel, Z, Karray, S and Lamure, M. Drug Reformulations and Repositioning in the 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).

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

6 Novac, N. Challenges and Opportunities of Drug Repositioning. Trends Pharmacol. Sci. 34, 267-272 (2013).

7 Persidis, A. Myths and Realities of Repositioning. a. Systematic DRPx-2015 Conference, Hanson Wade, Boston MA, USA October 21-23, (2015). http://systematic-drpx.com b. 4th Annual Drug Repurposing, Repositioning and Rescue Conference, Arrowhead, Chicago IL USA May 27-28 (2015). http://www.drugrepositioningconference.com/index.


Continued on page 57

non-profit and small biotech companies. These offerings range from consulting and fee-for-service technology platforms to 'in-house' discovery and development of RRRDx products[2]. The problem is that many of the DRPx companies have struggled to convince the pharmaceutical sector of the value of their service and product offerings. More success has been demonstrated by DRPx companies that have pursued their own drug candidate and drug product pipelines. This latter approach has resulted in a number of lucrative acquisitions by larger, more resource-rich companies, and has been perceived as a primary source of rapid value creation and accretion. However, such RRRDx product-focused companies usually lack significant start-up and growth capital resources. In order for new, emerging DRPx companies to attract capital they must create and execute on a viable business model that is not reliant on revenues derived from services provided to the pharmaceutical industry. They need to create a compelling narrative as well as a documented business case that clearly differentiates DRPx from *de novo*-derived DDD drug products. In this paper we discuss and present a comparative financial analysis for a *de novo*-derived drug versus a DRPx-derived drug, using Net Present Value (NPV) and Internal Rate of Return (IRR) calculations. We consider also the implications of our findings for DRPx companies focused on developing RRRDx products.

## Comparison of DDD versus DRPx metrics and models

A litany of woes has beset the DDD process employed by the pharmaceutical sector[8]. The process was conceived in the early 1960s and has remained unchanged over the past 50-plus years. Almost all other industries that utilise an R&D strategy have made frequent and sweeping changes; whereas the DDD protocols practised today continue to be risk-ladened, slow, costly and inefficient, as well as delivering products of questionable value[1]. For example, stratospheric risk is associated with any effort to bring a drug to market. The 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[9]. In addition, the failure rate of a drug candidate at each stage of DDD clinical trials, namely Phase I, II and III is 46%, 66% and 30% respectively[10]. The average time required from drug discovery to product launch remains at an eye-watering 12-15 years[11]. Finally, the total capitalised cost of bringing a new drug to market was recently calculated at a staggering $2.558 billion[12]. Some have argued that this is a gross overestimation[13,14], and a more realistic value is $1.778 billion[10].

The metrics associated with the DDD process are clearly problematic, but there is also a growing concern about the value proposition of the therapeutic drug products on offer. A number of factors have conspired to highlight this issue and they include:

**i. Drug safety:** Not all approved drugs stand the test of market pressures due to the scrutiny of pharmacovigiliance and post-market surveillance. In some cases approved drugs can be removed from the market because they manifest safety, effectiveness or economic problems. For example, from 1994-2015 the USA Food and Drug Administration (FDA) issued 215 'Withdrawal of Application' notices[15]. During that same time-period the FDA actually recalled 26 drugs from the US market predicated primarily on safety concerns[16]. This list includes well-known and widely-used drugs such as Baycol (Bayer AG, withdrawn 2001), Bextra (GD Searle, withdrawn 2005), Redux (Wyeth, withdrawn 1997) and Vioxx (Merck, withdrawn 2004). In the case of Vioxx alone, the litigation settlements which included patient lawsuits as well as criminal plea charges cost Merck more than $5.8 billion[17].

**ii. Drug effectiveness:** There is now a significant body of evidence that indicates individual patients diagnosed with the same disease indication respond differently to the same therapeutic drug[18]. For example, Spears and co-workers analysed the effectiveness of a number of different drug classes against major disease indications[19]. They found that most drugs ranged in effectiveness from 50-75% as determined by patient responses. The lowest patient responders occurred with conventional cancer chemotherapy (25%) whereas the highest percentage of patient responders was treated with Cox-22-inhibitors (80%). Therapeutic drugs were reported to be ineffective for 70% of Alzheimer, 50% of arthritis, 43% of diabetes and 40% of asthma patients[19].

**iii. Pricing:** As noted above, approved drug price points are determined by market forces that include drug safety and efficacy differentiation, market need, patient acceptance, sales and marketing strategy and IP position as well as individual R&D costs[20]. In many cases rampant R&D costs have been used by pharmaceutical companies to maximise prices charged to the patient/consumer. Unfortunately, even in such a favourable economic climate, only three in 10 approved drugs generate revenues that are at least equal to or greater than

average R&D costs[21]. In addition, pricing strategies are not as straightforward as in other industries. For example, RRRDx products should be subject to the same market forces as DDD-derived products, but the outcome is often nuanced and complex. One such case study is Tecfidera (Dimethyl Fumarate) marketed by Biogen. It was approved as a new indication to treat multiple sclerosis (MS) in 2013 and achieved stunning revenue sales of $2.91 billion worldwide in 2014[2]. Tecfidera is one of three recently-approved oral 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, and aggressive pricing by Biogen does not appear to have hindered sales[2].

**DDD productivity model**

All of the issues noted above raise the beguiling question of how to improve on such a quandary of problems? For more than 30 years the Center for the Study of Drug Development (CSDD) at Tufts University has pondered this matter and evaluated the R&D metrics of risk, time, cost and value associated with the DDD process[21]. The CSDD estimated late last year the cost of bringing a new drug to market at $2.558 billion[12]. This total dollar amount included $1.395 billion in out-of-pocket expenses, as well as $1.163 billion in capitalised costs. This latter item is the cost associated with an 'expected investment return' that investors forego while the drug is being developed. The estimate did not include an additional $312 million associated with lifecycle management costs after the drug is approved. The analysis was based on 106 randomly selected drugs from 10 major pharmaceutical companies that were developed during the period 1995-2007, and a 10.5 % cost of capital (CoC) was applied[22].

There was an immediate repudiation of the CSDD estimate, accompanied by suggestions that the cost was inaccurate and inflated[13,14]. Booth argued that the model was distorted since it was "biased towards Big Pharma programs"[14]. A more intense attack was propagated by the medical charity Medicins Sans Frontieres (MSF), which issued a statement stating that "if you believe that [cost of $2.558 billion] you probably believe the earth is flat!"[13]. In addition GlaxoSmithKline's CEO Andrew Witty was quoted as saying that "the figure of a billion dollars to develop a drug is a myth… and is used by the industry to justify exorbitant prices"[13]. MSF also exhorted that a more realistic cost estimate ranged from as little as $50 million up to $186 million if the cost of failed programmes was also taken into account. The latter cost was based on estimations obtained from the Drugs for Neglected Disease Initiative (DNDi)[23].

In 2010 Paul and co-workers proposed a comprehensive R&D model that estimated a capitalised cost per new drug launch[10]. This model has found fairly widespread acceptance due to its thoroughness and completeness. They argued that one of the critical issues facing the pharmaceutical industry was the problem of productivity, and concluded that without an increase in R&D productivity, the pharmaceutical industry cannot sustain sufficient innovation to replace lost revenues due to patent expirations. Based on the critical importance of this concept, they attempted an unambiguous definition of R&D productivity and presented a compelling model consisting of "the essential elements of contemporary drug discovery and development that account for the current cost of a new medicine, and discuss[ed] the rate-limiting steps of the R&D process that are contributing to reduced R&D productivity"[10]. They went on to define productivity as a relationship between the value of a New Molecular Entity (NME) or New Biological Entity (NBE) and the investment required to actually generate such an approved NME/NBE. Finally, they proposed a 'productivity relationship or pharmaceutical value equation' which was defined as:

$$P \quad \alpha \quad \frac{WIP \times p(TS) \times V}{CT \times C}$$

where P is R&D Productivity
WIP is work in progress necessary for a single new drug launch
P(TS) is the probability of technical success
V is value
CT is cycle time (in years)
C is cost (in US dollars)

The model was developed using R&D performance productivity data from 13 pharmaceutical companies, provided by the Pharmaceutical Benchmarking Forum as well as internal Lilly Pharmaceuticals project data. According to Paul each of these parameters can be considered on a per project or portfolio basis. Clearly, increasing

Continued from page 56

**8** 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.
**9** 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).
**10** Paul, SM et al. How to Improve R&D Productivity: the Pharmaceutical Industry's Grand Challenge. Nature Reviews: Drug Discovery, 9, 203-214 (2010).
**11** 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.
**12** Tufts Center for the Study of Drug Development. Cost to Develop and win Marketing Approval for a New Drug is $2.6 Billion. Press Release November 18th, (2014). http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study.
**13** Malipani, R. R&D Cost Estimates: MSF Response to Tufts CSDD Study on Cost to Develop New Drug. Doctors Without Borders, November 18th, (2014). http://www.doctorswithoutborders.org/article/rd-cost-estimates-msf-response-tufts-csdd-study-cost-develop-new-drug.

Continued on page 59

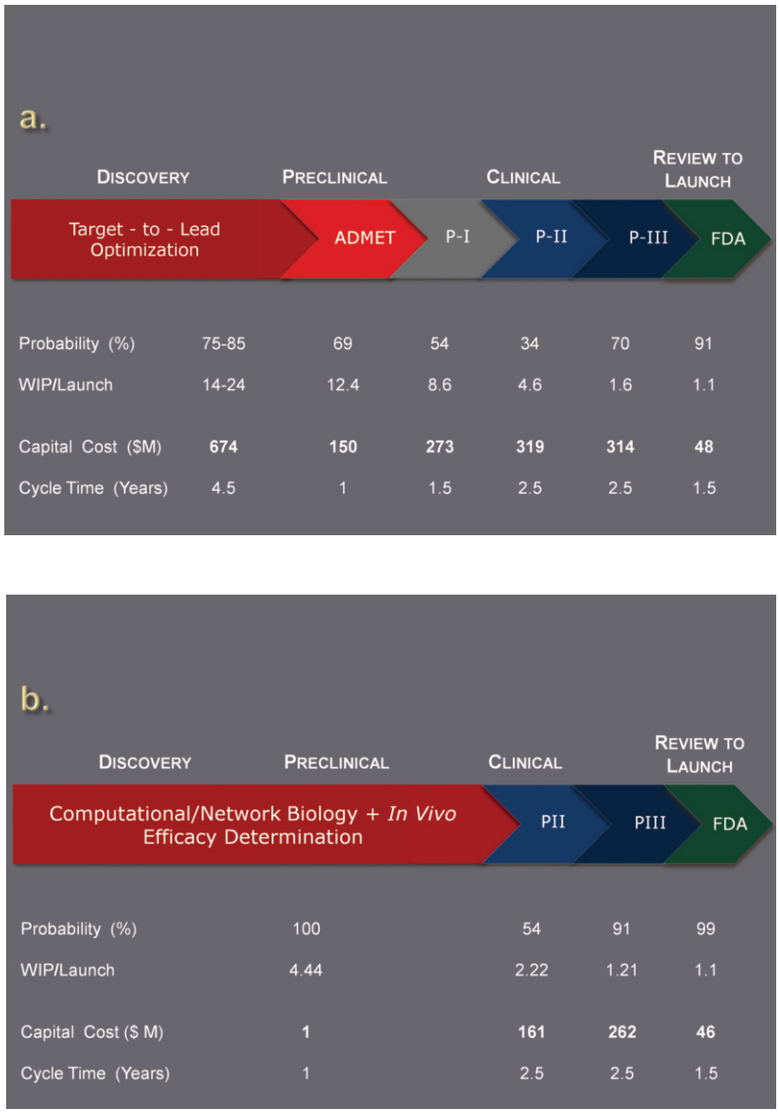


**Figure 1:** *De novo* DDD versus DRPx Productivity Models.
**1a (top):** Paul R&D Productivity Model for a *de novo* derived drug traversing a conventional DDD process that ensures one successful NME launch (adapted from[10]).
Probability: determined as a %, and is equivalent to the p(TS), which is the probability of technical success.
WIP/Launch: number of 'Work in Progress' projects necessary for a drug product.
Launch cost: Capitalised cost at an 11% capitalised cost.
Cycle Time: Time taken for each stage or phase shown in years.
**1b (above):** Kauppi and Naylor R&D Productivity Model for a DRPx derived drug. Terms as defined in Figure 1a

any of the components of the numerator relative to the denominator will increase productivity and *vice versa*. For instance, if one could decrease attrition, hence increase p(TS), for any given drug candidate or portfolio of drug candidates, at any phase in the process then P would increase accordingly. In a similar manner any given level of R&D investment, substantially reducing CT or C would also increase P. However, all of the components are linked together and changing any one element can adversely or beneficially impact other elements. Based on their comprehensive analyses they demonstrated that development (Phase I-III) requires ~63% of total costs whereas preclinical efforts account for ~32% of total costs per New Molecular Entity (NME) launched. They estimated that only 8% of NMEs will successfully traverse candidate selection to product launch. Finally the model required 9-11 molecules must enter clinical development every year in order to ensure a single NME is launched per year. Based on their Productivity Model and a CoC of 11% they estimated that it costs $1.778 billion per NME launch and on average this takes 13.5 years. All the key components of their findings are highlighted and summarised in **Figure 1a.**

### DRPx Productivity Model

Paul and co-workers argued that using their Productivity Model and starting from a baseline value for the estimated capitalised cost of a single NME, they could evaluate which operational parameters needed to be changed to enhance productivity and thus impact the key metrics of risk, time, cost and value. We took that cue and utilised their basic Productivity Model to create a DRPx Productivity Model. In the Kauppi-Naylor DRPx Productivity Model there are some significant differences and additional factors that need to be considered. As we have discussed previously, the conventional *de novo* discovery process is typically replaced by a computational and pathway/network biology platform in DRPx discovery[1]. A number of companies such as BioVista, CureHunter and Therametrics, use algorithmically augmented data mining to comprehensively query clinical trial datasets as well as other literature-derived data and information. The output from this type of analysis is a prioritised list of high probability RRRDx candidates that can be potentially used to treat a specific disease indication.

Each RRRDx candidate is accompanied by an 'Evidence Network' of specific information content that contains i) new disease indication(s); ii) safety/toxicity profile from patient outcome data derived from original clinical trials and published literature; iii) putative target for the new disease indication; iv) possible mechanism-of-action for the new disease indication; v) panoply of companion diagnostics specific for the RRRDx candidate defining elements such as safety, efficacy and patient stratification. Finally, each selected RRRDx

candidate should be subjected to an *in vitro* or *in vivo* efficacy determination using an appropriate cell/tissue/animal model. A successful RRRDx candidate can then be filed for IND status via the 505(b)(2) regulatory pathway, entering the clinical trials process at Phase II[3]. The RRRDx candidate must then traverse both a Phase II and a Phase III clinical trial before an NDA is filed, leading eventually to market launch. This is all captured and summarised in **Figure 1b**.

Perusal of the Kauppi-Naylor DRPx Productivity Model (**Figure 1b**) reveals some significant differences compared to the Paul Productivity Model. In the DRPx discovery phase, the dataset of potential RRRDx candidates comprises all known drugs and biologically active agents. For example, in the case of CureHunter this consists of ~247,600 compounds interrogated across ~11,600 defined disease indications[24]. Given the density and quality of data and information content associated with each prioritised RRRDx candidate and based on a discussion with other DRPx companies, the probability of technical success for the DRPx 'discovery' stage portfolio of candidates is estimated at 100%. In addition we calculated the cost of DRPx discovery at $225,000 per RRRDx candidate. This includes salaries for key personnel, overhead and efficacy determination studies all at a CoC of 11%, bringing the total discovery cost to ~$1 million (**Figure 1b**).

In terms of building out our model for the additional Phase II, Phase III and Approval stages, we utilised the lower rates of attrition in the DRPx process reported by Thayer[25]. She stated 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 for DRPx drugs advancing from Phase III to market increases to 65%, compared with only 50% for DDD drugs. This is reflected in our model where the improvement in the percentage of compounds advanced utilising DRPx versus traditional DDD impacts on p(TS), WIP/Launch, cost and cycle time. In terms of WIP/Launch projects this is reduced from 4.6 to 2.2 for Phase II and 1.6 to 1.1 for Phase III. As predicted by Paul, reducing attrition rates in Phase II and Phase III can significantly reduce costs[10]. Our model also reflects that reality and the capitalised costs for Phase II are reduced from $319 million down to $161 million for the DRPx process, and from $314 million down to $262 million, as seen by comparing **Figure 1a** versus **Figure 1b**. Conservatively, we have estimated that the cycle time remains the same, since we have limited data, but there is evidence that the cycle time for both Phase II and Phase III will be reduced in the DRPx process (see later for discussion).

**Value of DRPx Model**

A comparative analysis of the Paul Productivity Model (**Figure 1a**) representing *de novo* DDD versus the Kauppi-Naylor DRPx Productivity Model (**Figure 1b**) reveals that a well-devised DRPx strategy can add significant value to pharmaceutical company pipelines. In addition such an approach makes a compelling narrative for smaller DRPx-focused companies who are in the process of making decisions about the future strategic direction and focus. At a metrics level the specific issues that contribute to the value of DRPx based on the model are:

**i. 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)[10]. These poor success rates place tremendous pressure on the drug pipeline and hence pharmaceutical company productivity. Paul has also argued that reducing attrition rates (increasing p(TS) for Phase II and Phase III are the key impact changes to increase productivity[10]. Since RRRDx candidates have been either approved or shown to be safe in late stage trials they can enter the pipeline at Phase II, thus completely removing any attrition rate at discovery and preclinical stages. In addition, as discussed above the attrition rates for both Phase II and Phase III are significantly reduced in the DRPx process. 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.

**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 ~7.5 years for a DRPx drug, based on the Kauppi-Naylor Productivity Model (**Figure 1b**). We suggest this can be further reduced by innovation at the clinical trials stages predicated on the adroit use of companion diagnostics. However, it should be noted that 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 a cycle time of just four years[26].

**iii. Cost savings:** Previously, Persidis has suggested

Continued from page 57

**14** Booth, B. A Billion Here, A Billion There: The Cost of Making a Drug Revisited. Forbes /Pharma & Healthcare Online. November 21st (2014). http://www.forbes.com/sites/brucebooth/2014/11/21/a-billion-here-a-billion-there-the-cost-of-making-a-drug-revisited/.
**15** Gaffney, A. How Often Does FDA Withdraw Drugs Using Discontinuation Petitions? Very Rarely. Regulatory Affairs Professional Society. June 15th, (2015). http://www.raps.org/Regulatory-Focus/News/2015/06/15/22690/How-Often-Does-FDA-Withdraw-Drugs-Using-Discontinuation-Petitions-Very-Rarely/.
**16** ProCon,Org Thirty-Five FDA-approved Prescription Drugs Later Pulled from the Market. http://prescriptiondrugs.procon.org/view.resource.php?resourceID=005528.
**17** Feeley, J. Merck Pays $23 Million to End Vioxx Drug-Purchase Suits. BloombergBusiness. June 15th, (2013). http://www.bloomberg.com/news/articles/2013-07-18/merck-pays-23-million-to-end-vioxx-drug-purchase-suits.
**18** Vizirianakis, IS (Ed). Handbook of Personalized Medicine: Advances in Nanotechnology, Drug Delivery and Therapy. CRC Press/Taylor Francis Group. Boca Raton, FL, USA. (2013).
**19** Spear, BB, Heath-Chiazzi, M and Huff, JJ. Clinical Applications of Pharmacogenetics. Trends Mol. Medicine 7, 201-204 (2001).
**20** Persidis, A. The Benefits of Drug Repositioning. Drug Discov. World Spring Edition: 9-12 (2011).
**21** Kaitin, KI. Deconstructing the Drug Development Process: The New Face of Innovation. Clin. Pharmacol. Ther. 87, 356-361 (2010).

Continued on page 63

that the cost "to relaunch a repositioned drug averages $8.4 million"[20]. This appears to a rather conservative estimation and may be more applicable to simple, line-extension DRPx cases. Based on our model we estimate that the out-of-pocket cost is closer to ~$320 million, with a capitalised cost of $350 million, assuming that the RRRDx candidate has to only undergo Phase II and Phase III clinical trials. This represents a 80.3% 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 with its rich information content, as well as innovative execution in the clinical trials stage can dramatically affect the final cost of the DRPx process and reduce costs even further.

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.

## Financial analysis – DDD versus DRPx

We have discussed the Paul Productivity Model and the Kauppi-Naylor Productivity Model by considering the metrics of risk, time, cost and value. We now adapt both Models in order to provide financial insights into DDD versus DRPx. Paul originally identified out-of-pocket costs for each stage of the DDD process[10]. In order to more accurately portray the impact of the 13.5-year gap between the first invested dollar and the start of

positive cash flow, he also incorporated capitalised costs into the model. This latter analysis builds the time value of money into calculating the true cost of this process. For example, if a pharmaceutical company invests $50 million into the discovery process in year one, then according to the Paul Model it will not receive a return for 13.5 years, until the approved drug product reaches the market and records sales. The simplest way to think about the capitalised cost is to consider what that $50 million would be worth 'invested' in a bank account paying 10% interest annually. There is a calculation called future value which measures this, but for simplicity, think of multiplying the $50 million by 110% compounded annually 13.5 times. The capitalised cost for this $50 million investment is now $181.24 million! The Paul Model develops this premise and actually determines the level of expenditure at each stage of the discovery and development cycle and capitalises the cost of each stage based on how many years it is from the expenditure until positive cash flow. For example, expenditure at the early discovery phase would be outstanding for 13.5 years whereas the first year expenditure in Phase III clinical trials would be outstanding for only four years, as shown in the Cycle Time row in **Figure 1a**.

In this discussion we expand the analysis using a NPV and IRR approach in order to determine the revenue requirement of the resulting approved drug necessary to break even financially, given the front-end loaded expenditures and the significant time delay in receiving revenues due to the very lengthy approval process. We also compare and contrast the NPV and IRR values of DDD versus DRPx. In order to do this we have used the Paul Model, described above and summarised in **Figure 1a** for DDD, and our newly described Kauppi-Naylor DRPx Model we have recently developed and summarised in **Figure 1b**.

The NPV calculation is one that is typically utilised by the finance departments of corporations to aid them in allocating capital to determine optimal investment opportunities[27]. The NPV approach accounts for the time value of money, just as Paul did in presenting the capitalised cost model. The objective in our NPV analysis is to model expenditures as a function of time, as well revenues and when they are received and relate all these factors back to the start of the process at day one, ie present value. It is important to bear in mind that the nature of drug discovery front-end loads expenses and back-end loads revenues leading to burdensome expenses and revenues that are relatively muted. For example, $10 million spent on day one, costs the project in NPV $10 million, but $10 million in revenue received at the end of year 13 (assuming a CoC of 10%) is worth just $2,606,945. In other words the NPV analysis takes all cashflows for a project and discounts them back to day one using the determined cost of capital. If the calculation results in a positive NPV this indicates that the project/investment should move forward, and conversely a negative NPV outcome suggests the project/investment should be abandoned or modified. In a similar manner an IRR analysis models all of the project's cashflows over time and then enables the calculation of the rate of return on the capital investment[27]. The initial goal is to determine the value point of the IRR that makes the project/investment worthwhile pursuing. In the subsequent analysis if the target IRR is met then the project/investment should proceed.

We focused our initial analysis on the revenue needed from an approved drug in order to recoup R&D costs and financially break-even. The criteria we applied to the analysis was a CoC of 10%, a NPV=0 and an IRR of 10%. In our NPV and IRR analysis of the DDD process we employed the same up-front cost metrics and the timing of those expenditures as described by Paul (**Figure 1a**). We estimated that the revenues produced by the resulting approved drug and the timing of those receipts

**Table 1:** NPV and IRR values as determined for annual drug revenues ($100 million to $2 billion)

| DRUG REVENUE | *DE NOVO* DDD | DRPx DDD |
|---|---|---|
| $100 million – NPV<br>$100 million – IRR | (340.12)[a]<br>(2) | 43.58<br>12 |
| $200 million – NPV<br>$200 million – IR | (215.53)<br>4 | 308.20<br>22 |
| $300 million – NPV<br>$300 million – IRR | (90.94)<br>8 | 572.82<br>28 |
| $500 million – NPV<br>$500 million – IRR | 158.24<br>13 | 1,102.06<br>37 |
| $750 million – NPV<br>$750 million – IRR | 469.72<br>17 | 1,763.61<br>44 |
| $1 billion – NPV<br>$1 billion – IRR | 781.20<br>20 | 2,425.16<br>50 |
| $2 billion – NPV<br>$2 billion – IRR | 2,027.23<br>27 | 5,071.35<br>61 |

*The values were obtained using a cost of capital of 10%.*
[a] *In accounting terms ( ) represents a negative value.*

were determined by a period of exclusivity based on IP/Regulatory considerations[3]) to be 10 years post market launch. These analyses were carried out on an 'approved drug' ranging in hypothetical annual sales from $100 million up to $2 billion, and these data are summarised in **Table 1**. This type of sensitivity analysis creates a decision matrix for a pharma executive before they even embark on a new disease target. This is highlighted by the following consideration for a *de novo*-derived drug using the Paul Productivity Model with our back end revenue levels suggesting that in order to just break-even, the approved drug must produce annual cash flows of $263 million and assuming a net profit margin of 70%, total revenues of $375 million. This very high break-even revenue requirement greatly limits the disease targets that the pharmaceutical industry can profitably pursue.

In the case of the RRRDx-approved product, a very different outcome scenario is determined. As discussed above, in the DRPx process the search universe is only populated with candidate drugs that have been approved for use in humans, so the entire 4.5 years and $219 million of out-of-pocket discovery expense have been eliminated. Furthermore both Preclinical and Phase I clinical trials are also not necessary resulting in an additional saving of time, 2.5 years, and $190 million in out-of-pocket costs (compare **Figure 1a** with **Figure 1b**). This has all been replaced by algorithmically augmented data mining of the universe of clinical trials data in order to identify high probability candidates of known safe drugs for a new indication(s)[1]. One final advantage to such an approach is the enhanced IP/Regulatory exclusivity time period afforded to a RRRDx, which we conservatively estimate at 13 years. Based on all these consideration the break-even revenue level for a DRPx approved drug is $85 million and margins of $60 million for our period of exclusivity compared to the $375 million in revenue and $263 million in margin required to break-even on a *de novo* approved drug.

The IRR and NPV analysis summarised in **Table 1** for approved annual drug revenues ranging from $100 million up to $2 billion clearly

demonstrates the significant financial advantages accrued by employing a DRPx approach versus a DDD approach. Specific highlights include:

- Lower or eliminated front end costs based on selection criteria and mining research data using an algorithmic augmented approach.
- Shorter cycle time from project beginning to approved drug.
- Earlier receipt of positive cashflows because the drugs reach the market 5-6 years sooner.
- A longer period of exclusivity because time to product launch from patent date issuance is compressed.
- A greater percentage of advancement in Phase II and Phase III trials resulting in having to make expenditures on fewer compounds at these very expensive stages.

This significant improvement in ROI is necessary to cost-effectively build WIP pipelines and start to offset the revenue losses caused by the steady stream of patent expirations. The lower cost structure greatly expands the universe of diseases that can now be profitably targeted for drug development. This diminished cost model with a much improved risk profile should attract new investor money and provide some needed capital, talent and energy. Foundations can adopt a new model to back these DRPx projects and help speed cures to their constituents. Orphan diseases that have not had the investment necessary to support their limited populations may find a new wave of investment and support. What is really exciting is that we are leveraging technology and we are really in the early stages as it applies to big data analysis and algorithmic discovery to identify new disease targets for known safe drugs. One could speculate of the exponential improvements being made in the cost and time of sequencing the human genome or Moore's law as it applies to computing power and cost.

## Conclusions

The DRPx sector is populated by a small, but growing number of specialty companies and non-profit organisations. We have argued that in order for individual companies to be funded and successfully grow they must be less reliant on the 'benevolence' of the pharmaceutical sector. In addition they must consider the development of a credible narrative in order to raise capital to develop their own RRRDx product pipeline. We would suggest that the comparative analyses presented in the work makes a compelling case for the advantages of the DRPx versus *de novo* DDD process. A simple comparison of bringing a DDD drug candidate to market versus a DRPx drug candidate is remarkable in terms of the reduction of risk, time and cost for the latter, as highlighted in the Kauppi-Naylor Productivity Model. In addition the difference in break-even revenues required for *de novo*-derived DDD versus RRRDx candidate are illuminating. The break-even revenue level for a RRRDx approved product is $85 million with associated margins of $60 million. This opens up tremendous opportunity not just for small DRPx companies, but also Disease Foundations, other non-profits as well as advocacy groups representing Orphan diseases.

The advent of personalised/precision medicine has fuelled the transition of patients to consumers[28].This has led to a more demanding customer-base that requires a better, cheaper, personalised product. We have suggested that DRPx efforts can impact significantly on orphan, rare and neglected diseases, as well as providing therapeutic efficacy where none existed previously. 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 may be considered and contemplated with the more widespread adoption and use of DRPx.

As we have surveyed the DRPx landscape over the past year, we have been surprised at the perceived limited impact on the DDD process and product offerings. Every analysis we have done from business opportunity, to IP/Regulatory issues and now financial aspects of DRPx all indicate a sector confronted with tremendous opportunity. The question is how to leverage the opportunities and change the misperceptions? DDW

***David M. Kauppi*** *MBA is the Managing Director and President of MidMarket Capital Advisors LLC. His company provides investment banking and revenue enhancement consulting services for healthcare technology firms. He was also a business and financial adviser to CureHunter Inc, a DRPx company.*

***Dr Stephen Naylor*** *is Founder, Chairman and CEO of MaiHealth Inc, a systems/network biology level Diagnostics Company in the health/wellness and precision medicine sector. He is also a science and business advisor to CureHunter Inc, and the Chief Scientific Advisor to MidMarket Capital. Correspondence should be addressed to him at snaylor@midmarkcap.com*

Continued from page 59

**22** DiMasi, JA, Grabowski, HG and Hansen, RW. Cost of Developing a New Drug. November 18th, (2014). http://csdd.tufts.edu/files/uploads/Tufts_CSDD_briefing_on_RD_cost_study_-_Nov_18,_2014.pdf.
**23** Drugs for Neglected Diseases Initiative (DNDi). Research & Development for Diseases of the Poor: A 10-Year Analysis of Impact of the DNDi Model. December 5th, (2013). http://www.dndi.org/2013/media-centre/press-releases/dndi-rd-model/.
**24** Schonfeld, J. Computing a New Cure for Ebola or Alzheimer's in Four Minutes Flat! Systematic DRPx-2015 Conference, Hanson Wade, Boston MA, USA October 21-23, (2015). http://systematic-drpx.com.
**25** Thayer, AN. Drug Repurposing. Chem. & Eng. News 90, 15-25 (2012).
**26** Li, YY and Jones, SJM. Drug Repositioning for Personalized Medicine. Genome Medicine 4, 27-41 (2012).
**27** Schmidt, R. Understanding the Difference Between NPV and IRR. Property Metrics June 28th, 2013. http://www.propertymetrics.com/blog/2013/06/28/npv-vs-irr/.
**28** Naylor, S. What's in a Name? The Evolution of "P-Medicine". J. Precision Med. 2, 15-29 (2015).