Therapeutic Drug Repurposing, Repositioning and Rescue

Part III: market exclusivity using Intellectual Property and regulatory pathways

There is a growing consensus that Drug Repurposing, Repositioning and Rescue (DRPx) can impact the prescription drug industry for all concerned stakeholders. In part this is due to the fact that the pharmaceutical industry now accrues ~25% of its annual revenues from DRPx products. The DRPx approach appears to offer solutions to a myriad of problems that the industry faces. However, a major perceived hurdle in the successful execution and further uptake of DRPx concerns the Intellectual Property (IP) and regulatory labyrinth associated with such efforts. In this paper we discuss the exclusivity issues of a repurposed drug when using a combination of Intellectual Property and Regulatory pathways.

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Drug Repurposing, Repositioning and Rescue (DRPx) emerged in the early 1990s as a viable alternative to conventional Drug Discovery and Development (DDD)[1,2]. DRPx initiatives and endeavours currently play an increasing role in the DDD efforts of the pharmaceutical industry. It is estimated that the DRPx process accounts for more than 30% of new drugs and vaccines approved by the US FDA in recent years[3]. In addition Aris Persidis, President and Co-Founder of BioVista, has estimated that Repurposed, Repositioned and Rescued Drugs (RRRDxs) now generate ~25% of annual revenue for the pharmaceutical industry[4]. This growing impact on the revenue stream of the pharmaceutical sector has created a flurry of new activity and interest in DRPx. For example a new journal dedicated to DRPx entitled Drug Repurposing, Repositioning & Rescue has recently been launched[5], a book on the subject published[3], a series of annual conferences inaugerated[6] and a workshop proceedings sponsored by the USA Institute of Medicine was published last year[7]. In addition Cures Within Reach has just launched its web-based DRPx networking platform 'CureAccelerator'[8], and HM Pharma has recently introduced a new, DRPx 'Discontinued Drug and Candidate Database'[9].

Much of this activity has been perpetrated by dedicated DRPx non-profit and small biotechnology companies. During the past 20-25 years at least 67 DRPx non-profit and companies have been created. In that time period 11 of those companies were acquired for a total acquisition cost of $2.38 billion. Currently there are at least 38 companies engaged in active DRPx efforts, and ~65% of them are focused on developing robust RRRDx pipelines and marketing approved drugs[2].The advantages that accrue from DRPx efforts are even more compelling when considering the market potential of a RRRDx. Such RRRDx price points are determined by the same market forces as a conventional DDD drug, and include drug safety and efficacy differentiation, market need, patient acceptance, marketing strategy and IP position[10]. Thus a RRRDx has the same possibility to achieve blockbuster status as a *de novo* derived drug. We have highlighted this phenomenon previously by compiling a 'Top 10' list of current mini-blockbuster (~$0.5 billion/year in sales) and blockbuster (>$1 billion/year in sales) RRRDxs[2]. This compendium of RRRDxs includes Evista, Gemzar, Proscar, Propecia, Revlimid, Revatio, Rituxan, Tecfidera, Thalomid, and Viagra[2]. It is noteworthy that all the drugs listed were developed and are sold by large pharma or large biotech companies. The Top 10 mini-blockbusters and blockbusters have produced a total of ~$12.89 billion in peak annual sales alone. Thus it is not surprising to learn that DRPx constitutes anywhere from 10-50% of current R&D spending, and is a determinant factor in the life cycle management of pharmaceutical products[2].

The numerous benefits of DRPx are clear and well documented[1-3,7]. DRPx can result in new sales and market opportunities for shelved or abandoned compounds/drugs. Plus additional investigation and 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. 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[10]. In particular RRRDx market exclusivity is of paramount importance and can be adequately achieved by a combination of thoughtful IP and regulatory strategy efforts executed via an appropriate business model. This third and final paper in the series discusses these issues and describes various approaches to achieve market exclusivity. The primary descriptions discussed in this paper focus on USA-driven processes, but many of the general IP and regulatory issues are somewhat similar in other major global pharmaceutical regions such as Europe, Japan and China.

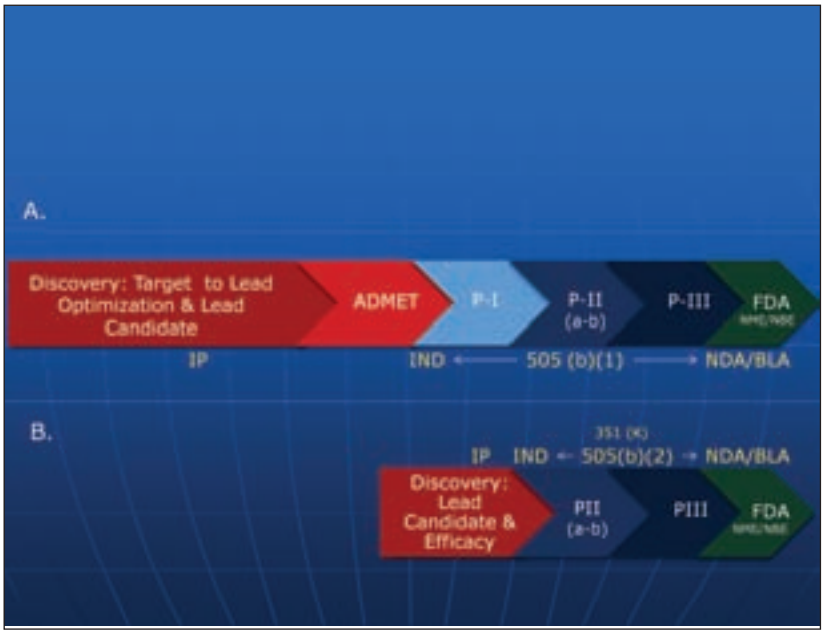

Figure 1
Comparison of the IP and regulatory processes in *de novo* DDD versus DRPx
A. DDD
B. DRPx

De Novo DDD & DRPx

De Novo DDD is a well described, defined and regulated process[11]. The initial discovery phase is both costly, time consuming and fraught with dead-end efforts. Paul and co-workers have estimated that the cost and cycle-time for the discovery process in order to successfully launch a single drug is $674 million and 5.5 years respectively[12]. Identification of a 'Lead Candidate' typically results in a whirl of IP filing activity on behalf of the pharmaceutical company. The lead candidate is then subjected to *in vitro* cellular and animal testing to determine its absorption, distribution, metabolism, excretion and toxicity (ADMET) profile. Paul has suggested that this 'Pre-Clinical' phase costs on average $150 millon and takes approximately one year to complete in order to ensure a single candidate gets to market[12]. Successful completion of the pre-clinical phase then necessitates the filing of an Investigational New Drug Application (IND) with the FDA. The completed IND is required in order to administer a drug or biologic agent to patients in human clinical trials. The drug candidate is evaluated in humans via a series of clinical trials (Phase I-III) as outlined in section 505(b)(1) of the US Federal Food, Drug and Cosmetic Act of 1938. After successful completion of the clinical trials the drug candidate is

subject to a New Drug Application (NDA) or "iologic License Application (BLA) depending on whether the compound is a chemical or biological entity. It should be noted that some biologics are also simultaneously regulated under the US Federal Public Health Service Act of 1944, but this is outside the scope of this article. Finally upon NDA or BLA approval, the New Molecular Entity (NME), or New Biological Entity (NBE) is allowed to enter the marketplace and be prescribed and sold to patients/consumers. A somewhat similar process is required by regulatory agencies in other countries and this is discussed below. All this is captured and summarised for the DDD process under FDA regulatory guidelines in **Figure 1a.**

The DRPx process is remarkably similar to that described above for DDD, and is encapsulated in **Figure 1b**. However, the discovery stage is significantly truncated since both computational biology and phenotypic screening tools provide rapid platform approaches[1,13]. Since the lead candidate has most likely been subjected to safety and toxicological evaluation for the original indication, then the Pre-Clinical phase only requires a demonstration of efficacy for the new indication in either a cell or animal model system. Assuming that the lead candidate exhibits efficacy for the new indication then an IND is filed with the FDA. The major difference is that a RRRDx is subject to the 505(b)(2) process, which allows information from previous studies to be used in the evaluation of the drug candidate. Hence the lead candidate can typically enter the clinical trials process after Phase I, normally at Phase IIa. In the case of biologics, since the DRPx process is so new, the regulatory approval is via a different route for many biologics. Under the Biologics Price Competition and Innovation Act (2010) a biosimilar (or biologic for a new indication) is evaluated using the 351(K) process. In either case successful clinical trials lead to either an NDA or BLA and the repurposed drug/biologic enters the market.

There are numerous differences when comparing DDD to DRPx and in all cases affords benefits to the RRRDx over the *de novo* derived drug. This is all summarised in **Table 1**. For example Paul has

suggested that the cost of bringing a *de novo* drug to market is $1.778 billion[12]. We estimate that the cost of launching a RRRDx is approximately $300 million, a saving of ~85%[1,2]. In a similar manner, the time and risk of bringing a RRRDx to market is also significantly reduced when compared to a *de novo* derived drug. The differential financial analysis of DDD compared with DRPx is even starker. The Net Present Value (NPV), at an estimated 10% cost of capital, of a *de novo* drug, with calculated annual market sales of $300 million, is negative $795 million and an Internal Rate of Return (IRR) of negative 3.2%. In contrast a $300 million RRRDx has a NPV of a healthy $280 million with an IRR of 15.0%. Similar calculations for a *de novo* drug with $2 billion annual sales realises a NPV of $776 million with an IRR of 15.6%, but an equivalent RRRDx returns a NPV of $4.78 billion and an IRR of 43.6%! Finally, at a 10% cost of funds, we calculate that the breakeven revenue requirement for a *de novo* drug is a revenue run rate of $1.2 billion per year, whereas for a DRPx drug, the breakeven revenue run rate is $195 million (see **Table 1**).

This differential analysis highlights the potential advantages of a DRPx approach, but does not take into consideration the fact that once a *de novo* drug or RRRDx reaches market it is then simply subjected to conventional market forces. One example is Tecfidera (Dimethyl Fumarate)) 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 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. Analysts are predicting that Tecfidera will dominate the market share of oral MS therapies and estimate annual sales reaching ~$3.5 billion by 2017[14]. Clearly there are significant advantages to DRPx from a cost, time, risk and financial perspective. Hence it is imperative that a well thought through strategy predicated on IP and regulatory considerations is executed on in a timely and efficient manner.

Table 1: Comparative analysis metrics of *de novo* DDD versus DRPx DDD
[a] Annual sales

	***de novo* DDD**	**DRPx DDD**
Time (Years)	13.5	6.5
Cost (US $)	1.78 billion	300 million
Risk (%)		
Discovery success	< 5	100
Phase II to Launch	10	25
Phase III to launch	50	65
Financials		
NPV -$300M ($)	(-795 M)	280 M
IRR -$300M (%)	(- 3.2)	15.0
NPV -$2B ($)	776 M	4.78 B
IRR -$2B (%)	15.6	43.6
Breakeven ($)[a]	1.2 billion	195 million

Intellectual Property exclusivity

Based on the process flow described in **Figure 1**, the first important step in the DDD product exclusivity quest is the filing of IP. The USA Patent and Trademark Office (USPTO) recognises three major types of IP. Utility patents are issued for a new invention and exist for a period of 20 years. Design patents are granted for an original design and last 14 years, whereas plant patents are issued for asexual plant production and are granted for 20 years. The vast majority of patents issued are in the form of utility patents. These are granted for the invention of a 'new and useful process, machine, manufacture, or composition of matter, or a new and useful improvement'. In general this permits its owner to exclude others from making, using or selling the invention for a period of up to 20 years from the date of patent application filing[15]. There are four principal categories of utility patents namely i) composition of matter (COM); ii) process or method of use (MOU); iii) machine; and iv) manufacture. In the case of both DDD and DRPx, it is COM and MOU patents that are primarily prosecuted. However, when the US Congress established the existing legal infrastructure for drug patents and regulatory exclusivity it designed the system to encourage and promote the

DDD of new drugs. The system as it exists today does not provide a structured framework for the discovery of new indications for existing drugs. Thus a patchwork of approaches has arisen to facilitate the protection of RRRDxs, and has led to the perception that such approaches are either difficult or not possible to execute on in an efficient and useful manner. This is clearly not the case, for example there exists a variety of options for DRPx candidates in terms of IP protection and these options are discussed below.

Composition of matter: It is widely accepted that the strongest patent protection is provided by COM patents[16]. These patents can be predicated on:

- The active pharmacological ingredient (API). In the case of DRPx, this is not a typical option, since the original API is normally being used for a new indication. However, a novel crystallisation, salt formation or unique structural polymorphisms are all possible.
- Novel formulation that promotes patient compliance through reduced dosing or ease of use.
- Unique delivery that facilitates a new route of API administration
- Stereoselective production of a specific enantiomer of a racemic mixture.
- Deuterated analogs of the API.
- Combination therapies of known API compounds.

In the case of DDD products, patent filings often occur early in the discovery cycle of the candidate drug (see **Figure 1a**). This can result in a rather limited life-span of COM patent protection for the DDD marketed drug. In contrast, the DRPx process (**Figure 1b**) enables a later stage filing and significantly increases the patent protection period of the DRPx marketed drug. However, the success of such a strategy will depend on the availability of generic products that can be substituted by off-label prescription use by individual physicians. Clearly, the optimal scenario for a COM position is when the API of the DRPx product is solely approved for the newly-patented indication via one

of the options described above. This situation is facilitated by the fact that for a generic product to gain regulatory approval it must be an exact copy of the approved indication. Since there are no other approval possibilities to allow generics on to the market then "there is no opportunity to 'skinny label' the generic product (ie copying only the off-patent indications on to the label, but leaving the patented new indication off the label) and attack the repositioned product through off-label use"[16].

Method of use: These patents cover the use of a RRRDx for a new specific disease indication, or a method of dosing a patient. It has been suggested often that MOU patents are simply incremental in nature and therefore have limited value. However, based on numerous examples this is clearly a misinterpretation of the facts. Given the right circumstances and the appropriate strategy, a MOU can be just as effective as a COM patent in protecting RRRDx product exclusivity for 20 years as discussed below.

Patent extension: In addition to the 20-year exclusivity protection afforded by COM and MOU patents, it is also possible to claim an additional five-year extension in the USA. The Drug Price Competition and Patent Term Restoration Act (aka Hatch-Waxman Act) of 1984 grants applicants an additional five years to compensate for any undue delays caused by the FDA approval process[17]. The right to a patent extension is predicated on a number of factors including the time a drug product was assessed in the approval process. However, it should be noted that the extended patent life cannot exceed 14 years from the time of approval for the RRRDx product by the FDA. Nonetheless such an approach can be extremely useful in the armament of DRPx product exclusivity.

There is a wide-ranging misperception that RRRDx products cannot readily achieve a defensible exclusivity position in the marketplace. This appears to be a somewhat paradoxical assessment since the pharmaceutical sector business model is predicated on drug products protected by patent/regulatory exclusivity, and yet ~25% of annual revenue streams stem from DRPx[4]. In addition there appears to be a considerable fact-based portfolio of examples that indicate that such a misperception is patently false. For example there are numerous cases of successful and/or significant RRRDxs that have been awarded COM patent protection. Biogen was granted a number of COM patents for its blockbuster drug Tecfidera delivered in the form of a delayed release capsule for the treatment of MS[18]. Ceptaris (a NeXeption company) reformulated the nitrogen mustard Mechlorethamine (Valchor) as a topic gel for the treatment of early stage mycosis-fungoides-type cutaneous T-cell lymphoma[2,18]. The drug and the company were acquired by Actelion for $250 million in 2013, predicated on their COM patents and of course successful Phase II clinical trials. Even more recently, Novartis received fast-track approval for its COM protected combi-therapy LCZ-696. The drug is a one-to-one co-crystallised mixture of Valsartan and Sacubitril used in the treatment of heart failure[19]. In the case of MOU patented-protected RRRDxs, numerous mini-blockbuster and blockbuster drugs acquired market exclusivity using this approach. The list includes Retrovir (MOU patent for AIDS indication expired 2005); Propecia (MOU patent for male pattern baldness expired 2006); Thalomid (MOU patents for leprosy and multiple myeloma expire all the way through to 2020); and Viagra (MOU patent for erectile dysfunction expires in 2019)[16,18]. In the latter case an MOU protected product generated ~$22 billion in global sales during the period 2003-2014[20].

There is a concern that the availability of off-label prescribed generic drugs tends to invalidate any viable IP strategy for RRRDx products. Clearly, the aggressive marketing of generic drug companies cannot be ignored. However, while the FDA does not prohibit physicians from prescribing drugs off-label, it does prevent pharmaceutical companies from marketing their drugs for off-label uses[21]. Indeed in the past several years (2009-2014) most of the major pharmaceutical companies including Pfizer, Merck, GSK, Sanofi, J&J, Lilly, AstraZeneca, Abbott and Amgen have agreed to pay more than $13 billion to resolve US Department of Justice allegations of fraudulent marketing claims/practices primarily involving off-label indications[22]. Thus if there is no promotion by the pharmaceutical companies involving a new indication for an old drug, then most physicians will remain ignorant of potential new uses for generics. Another emerging impediment to prescribing generics off-label, at least in the USA, is the payers. Almost all payers now limit their coverage of prescription drugs to indications that are approved by the FDA. They utilise sophisticated monitoring capabilities to enforce indication-based restrictions on prescribing drugs[21]. This all creates significant barriers to the prescribing of a generic drug for a new indication that is not on-label and for the patient to be reimbursed.

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In a final optimistic note of irony, the generic drug company blockade of RRRDx IP is being challenged by no less than one of the world's largest pharmaceutical company. Pfizer originally filed COM patents for Lyrica (API-pregabalin) in the treatment of epilepsy and general anxiety disorder. They subsequently filed MOU patents for repurposed Lyrica in the treatment of pain and fibromyalgia and this was approved in late 2004[18]. In a very recent development Pfizer has written to physician groups in the UK "to warn them that prescribing generic versions of its Lyrica medicine – specifically for treating pain – would violate its patent"[23]. The company took these steps after its original COM patents expired in July 2013. "Pfizer believes the supply of generic pregabalin for use in the treatment of pain while the pain patent remains in force in the UK would infringe Pfizer's patent rights," Ruth Coles, the Pfizer legal director in the UK, writes in the letter. "This would not be the case with supply or dispensing of generic pregabalin for non-pain indications[23]." The entrance of a large pharma into this battlefield suggests that the issue of weak IP viability for RRRDx products because of generic drug off-labelling is far from over.

Regulatory exclusivity

In 1984 the US Congress passed the Hatch-Waxman Act to protect and enhance the needs of the generic drug industry. The generic drug companies had originally complained that after a patent had expired on the originator drug, it then took a number of years before the generic product could enter the market. Thus a 'safe harbour' protection provision was written into the Act so that generic companies could perform clinical studies on the originator before patent expiration. The resulting data could then be used for an Abbreviated New Drug Application (ANDA) required by the FDA in order to demonstrate bioequivalence of generic drug to the originator drug. The safe harbour provision has also been expanded to include research in the use of RRRDx products where the COM patent is actually owned by another company. Numerous subsequent court rulings, including the some by the US Supreme Court, have affirmed the use of the safe harbour provision for RRRDxs, and the use of such data in filing IND or NDA documents[17].

The importance of the Hatch-Waxman Act cannot be overstated for DRPx exclusivity opportunities. It provides not only provides the safe harbour provision, already discussed, but also allows data and RRRDx product exclusivity. Indeed the exclusivity periods afforded by the Hatch-Waxman Act may be of such significant length as to justify bringing a RRRDx product to market just predicated on regulatory considerations alone. Smith and others have suggested that regulatory exclusivity for such products can be characterised into three basic types that includes NCE exclusivity, New Use/Formulation exclusivity and Orphan drug exclusivity[3,16,21].

NCE exclusivity: A shelved drug candidate has obviously not received prior FDA approval for sale in the US market. Hence the API of the shelved drug is eligible for NCE exclusivity. This exclusivity prevents any other drug manufacturer from using this safety and efficacy data for a period of five years. In addition the DRPx developer also has a four-year period without the possibility of facing a challenge posed by a competing ANDA or 505(b)(2) application from a competitor.

New use/formulation: This type of exclusivity applies to a RRRDx that includes significant changes to the originator, such as a change in disease indication, dosage strength, formulation or delivery method. New use/formulation exclusivity is similar to NCE exclusivity but is reduced from five years down to three years. However there is waiting period for other competitors to file an ANDA or 505(b)(2) application.

Orphan drug exclusivity: The Orphan Drug Act of 1983 was passed by the US Congress in order to facilitate the development and commercialisation of therapeutic agents to treat rare diseases, commonly referred to as orphan diseases[3]. In the USA an orphan disease is defined as a condition that affects less than 200,000 individuals nationwide. Market exclusivity for an orphan disease drug is particularly attractive regardless of whether the application was filed under 505(b)(1) or 505(b)(2). It consists of a seven-year period that begins once the drug has been granted approval by the FDA, and is independent of the drugs current patent status. A similar provision exists for pediatric drugs (under the Best Pharmaceuticals for Children Act of 2002). This allows for an additional six-month exclusivity period.

The regulatory exclusivity opportunities for RRRDx products are real and clearly defined as noted above. However, it is also possible to use such approaches in other creative and impactful ways. As an example Evista (Raloxifene) was a Lilly drug used in the treatment of osteoporosis in postmenopausal women. In 2007 it was repur-

posed 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]. This prevented generic competition from entering the market and allowed Lilly to continue to accrue global annual revenues for the drug of >$1 billion.

Conclusions

Facts belie the perception. It is evident that a thoughtful IP and regulatory strategy can lead to successful repurposed drug exclusivity. At present the tools available represent a patchwork of possibilities since the current processes were not designed to encourage new disease indication discoveries for existing drugs. However, it appears that the time has arrived when the (mis)perceptions of repurposed drug exclusivity are replaced with the conception that repurposed drug exclusivity is readily achievable. Finally, given that financial models for DRPx show reduced risk and solid returns on investment for the pharmaceutical manufacturer, we expect systematic use of DRPx technologies to grow rapidly. Simultaneously the physician's armamentarium will increase as will the treatability of a broad range of diseases and patient populations with currently unmet therapeutic needs. Thus, in the final analysis, DRPx with reasonable IP/Regulatory protection has the technical capacity to maintain industry margins while lowering the cost of care and improving it for all – the current major goal of the entire health care industry and all stakeholders in it: Patients, Physicians, Pharma and Payers.

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