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Drug repurposing

# Repositioned drugs: integrating intellectual property and regulatory strategies

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**Successful repositioning of a drug product depends on carefully considering and integrating both intellectual property and regulatory exclusivities. Patent strategies directed to protecting new formulations, indications and methods of use, when combined with strategically repositioned products, can provide effective and long lasting product exclusivity even where the underlying API, and the original formulations, indications and methods of use are off-patent.**

## Introduction

Drug developers both large and small have looked to drug repositioning (also sometimes referred to as 'repurposing') as a cost effective reduced-risk strategy for developing new drug products. Although repositioning can mean new life for shelved or abandoned drugs that have never been on the market, or extended life for marketed drugs via new indications or formulations, commercial success of a repositioned drug will depend on achieving effective market exclusivity through a combination of intellectual property and regulatory exclusivity.

Drug repositioning has become a mainstream drug development strategy for major pharmaceutical companies as a result of the confluence of several market forces affecting those companies. Those market forces include the need to reduce development costs and development risk, the need to speed development cycles, and the need to implement

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aggressive product life cycle management to try to preserve market share in the face of generic competition. Repositioned drugs can offer major pharmaceutical companies a short development cycle means to quickly fill crucial drug pipelines as marketed products continue to fall off the 'patent cliff.'

Drug repositioning has also become a major strategic business goal for many smaller biotechnology and specialty pharmaceutical drug development companies. These smaller companies have been facing a financial crisis driven in large part by investor distaste for high risk, high cost, and long timeline drug development programs. The right drug repositioning program can provide a smaller company with a marketable drug product in the relative near term resulting from a reduced risk, reduced cost and reduced development time program. Such drug development programs can attract venture capital and other investment where higher risk, higher cost, longer term programs cannot.

Table 1 shows several examples of repositioned drugs grouped in accordance with the strategies discussed in this article.

## Patent exclusivity

It is generally understood that the strongest patent protection is provided by patents that protect the composition of matter of the product. The strongest composition of matter patents typically cover the active pharmaceutical ingredient (API)

**Table 1. Repositioning strategies and corresponding examples [8–10]**

Product	Company	Original indication	Repositioned indication	Exclusivity
<b>New indication for previously shelved product</b>				
<b>Retrovir (AZT, zidovudine)</b>	ViiV Healthcare (GSK/Pfizer)	Cancer (shelved in 1960s; anti-retroviral effect noted in 1974)	AIDS (100 mg capsule approved in 1987)	Method of use patent for AIDS indication expired in 2005; ANDA patent challenge in 1991 (failed); Generics entered market in 2005
<b>Viagra (sildenafil)</b>	Pfizer	Pulmonary arterial hypertension (ED indication launched before this indication; see Revatio)	Erectile dysfunction (25/50/100 mg tabs approved in 1998)	Composition of matter patent expires in 2012, use patent for erectile dysfunction expires in 2019. Could be subject to off-label use of generic Revatio (20 mg tab) starting in 2012
<b>Thalomid (thalidomide)</b>	Celgene	Morning sickness (withdrawn from market due to birth defects)	Erythema nodosum leprosum (ENL), a side effect of leprosy; Combined with dexamethasone for treatment of multiple myeloma	Orphan drug exclusivity through 2013. Patents covering methods of treating ENL, multiple myeloma and implementing the FDA-mandated safety program expire on various dates through 2020.
<b>Mozobil (plerixafor)</b>	Genzyme	Inhibitor of HIV infection (never launched)	Used in combination with G-CSF for mobilization of haematopoietic stem cells in treatment of multiple myeloma	Composition of matter patent expires in 2013; Method of use patents for mobilization of haematopoietic stem cells expire in 2023; NCE Exclusivity expires in 2013 and Orphan Drug Exclusivity expires in 2015
<b>New formulation for existing product</b>				
<b>Aplenzin (bupropion HBr)</b>	Sanofi-Aventis	Depression (For API HCl salt, none for HBr salt)	Depression (once a day dosing, higher stability and bioavailability, approved 2008)	Composition of matter and use patents will expire in 2026
<b>Vivitrol (naltrexone)</b>	Alkermes	Opioid addiction and alcohol dependence (50 mg tab; approved 1984)	Prevent opioid dependence relapse and alcohol dependence (once per month extended release injectable; improved patient compliance; approved 2006)	Use patents expire in 2029. Regulatory exclusivity for relapse indication will expire in 2013
<b>New indications for existing product</b>				
<b>Cymbalta (duloxetine)</b>	Lilly	Stress urinary incontinence (approved in EU in 2004, not approved in US), Major depressive disorder (MDD) (approved 2004)	Maintenance treatment of MDD (approved in 2007); general anxiety disorder (GAD) (approved in 2007); fibromyalgia (approved in 2008); maintenance treatment of GAD (approved in 2009); chronic musculoskeletal pain (approved in 2010)	Latest method of use patent, for treating fibromyalgia, expires in 2019. Drug will go off patent for other indications by 2014. Last regulatory exclusivity (for GAD) expires in 2012
<b>New formulation and indications for existing product</b>				
<b>Propecia (finasteride)</b>	Merck	BPH (Proscar 5 mg tabs; generics available since 2005)	Male pattern baldness (Propecia 1 mg tabs; generics not available)	Method of use patent for BPH expired in 2006. Method of use patents for MPB will expire in 2013.
<b>Zyban (bupropion HCl)</b>	GSK	Depression (Wellbutrin, 1985; Wellbutrin SR, approved in 1996)	Smoking cessation (Wellbutrin SR 150 mg approved in 1997)	Sustained release formulation patent will expire in 2013

<b>Silenor (doxepin)</b>	Somaxon	Depression and/or anxiety (10, 25, 50, 75, 100 mg capsules, approved 1986)	Insomnia (low dosage 3 and 6 mg tablets, approved 2010)	Last use patent will expire in 2027 (label requirement to take at least 3 hrs after meals); Regulatory exclusivity expires in 2013
<b>Bildil (hydralazine &amp; isosorbide dinitrate)</b>	Nitromed	Hypertension (25, 50 mg tab)/vasodilator (20 mg tab)	Heart failure (37.5/20 mg tab; approved in 2005)	Use patents expire in 2020. Has experienced competition from combined use of inexpensive generics off label
<b>Revatio (sildenafil)</b>	Pfizer	Pulmonary arterial hypertension (But Viagra approved first for erectile dysfunction) (Viagra 25/50/100 mg tabs)	Pulmonary arterial hypertension (20 mg tab, approved in 2005; IV formulation approved in 2009)	Patent and regulatory exclusivity both expire in 2012. Potential use of generic Revatio off label for ED in 2012.

contained in the product, followed by patents that cover unique formulations and delivery mechanisms. Unfortunately, because the composition of matter inventions and patent filings for the API and original formulations usually occur early in the long development cycle of a new drug product, the patent life available after the product reaches the market for the most valuable composition of matter patents can be very short lived when compared to the time and investment required to bring the product to market.

However, new composition of matter protection may be available for repositioned drugs, for example, where the repositioned drug product incorporates a new patentable chemical entity or formulation, patentable delivery mechanism, or patentable combination of APIs. The success of such composition of matter patents in protecting the repositioned drug product will depend in large part on the availability of generic products that can be substituted through off-label use to achieve the same therapeutic result as the repositioned product.

Method of use patents that cover, for example, the use of a pharmaceutical product for a specific indication or cover a method of dosing a patient are often dismissed as incremental protection that is not as effective as a composition of matter patent in protecting a drug product. However, given the right set of circumstances, a method of use patent can be as effective as a composition of matter patent in protecting a repositioned drug product.

The strongest use patent scenario occurs when the API in the repositioned product is only approved for the newly patented indication and is not otherwise on the market in a branded or generic form suitable for substitution for the repositioned product. Effective protection arises because for a generic product to enter the marketplace, the generic manufacturer must copy the only approved indication (the patented repositioned indication!) onto the label, which will lead to patent infringement of the use patent. Because there are no other approved indications available as a basis to allow a generic product onto the market, there is no opportunity to 'skinny label' the generic product (i.e. copying only the off-patent indications onto the label, but leaving the patented new indication off the label) and attack the repositioned product through off-label use. As it is probable that use patent covering the new indication will not be filed until late in the drug development program when the new use is discovered, the use patent can offer protection in the marketplace for a relatively long period of time after product approval.

In addition to the normal 20 year term for a patent, a patent covering a drug product in the United States may be eligible for up to 5 years of patent term extension available under the Hatch–Waxman act [1] to compensate for any delay in obtaining FDA approval. The right to a patent term extension is based on a facts and circumstances test that looks

at, among other things, the length of time a drug product required to work its way through the drug approval process, the diligence used by the patentee in obtaining approval of the product, and whether or not the patent or API had received a prior extension. Careful consideration needs to be given to how an extension will be used and which patent covering the drug product will be extended.

### Regulatory exclusivity

Although a strong patent position will be the best approach to ward off competition for a repositioned drug product, the data and product exclusivities provided by Hatch–Waxman [1] may also be relied on to effectively protect the repositioned product in the United States. Even in the case where there is no patent protection for the repositioned product, the length of regulatory exclusivity accorded a repositioned drug may, by itself, be sufficient to justify the limited investment required to bring a reduced risk repositioned drug product to market.

Regulatory exclusivity most probably suitable for repositioned drug products in the United States can be characterized into two basic types: New chemical entity (NCE) exclusivity and new use/formulation exclusivity.

### NCE exclusivity

NCE exclusivity attaches to a drug product upon FDA approval if that drug product contains an API that has not received prior FDA approval for sale in the United States. An API is deemed to be a NCE so long as that API has not already been approved as a marketed drug product, regardless of how long the API has been in development. NCE exclusivity will prevent another drug manufacturer from relying on the innovator's safety and efficacy data for a period of at least 5 years from approval of the reference listed drug product. Under Hatch–Waxman, the FDA is prevented from accepting the filing of an abbreviated new drug application (ANDA) [2] for a generic version of the reference listed drug or a 505(b)(2) [3] new drug application for a modified version of the reference listed drug during the first 4 years of the exclusivity period, and from approving such ANDA [2] or 505(b)(2) application earlier than 5 years after the start of the exclusivity period.

In the event the reference listed drug is covered by a patent listed in the Orange Book, then the ANDA or 505(b)(2) application must include either a certification that the applicant will wait to market the generic or modified version of the drug until the listed patent expires, or a certification that the listed patent is invalid and/or not infringed by the generic or modified version of the drug (commonly referred to as a 'Paragraph IV' certification). The filing of an ANDA or 505(b)(2) application with a Paragraph IV [4,5] certification that the listed patent is invalid and/or not infringed amounts to a patent challenge that allows the owner of the reference

listed drug to immediately file a patent infringement suit against the applicant. One effect of a patent challenge if suit is filed is to automatically stay the approval of the application for an additional 30 months after the certification is made, which can result in an exclusivity period of about 6 years regardless of whether the listed patent is held to be invalid or whether the generic or modified product is determined not to infringe the reference listed drug. Of course, a verdict that a listed patent is valid and infringed by the generic or modified product should prevent approval of that product until the patent expires.

### New use/formulation exclusivity

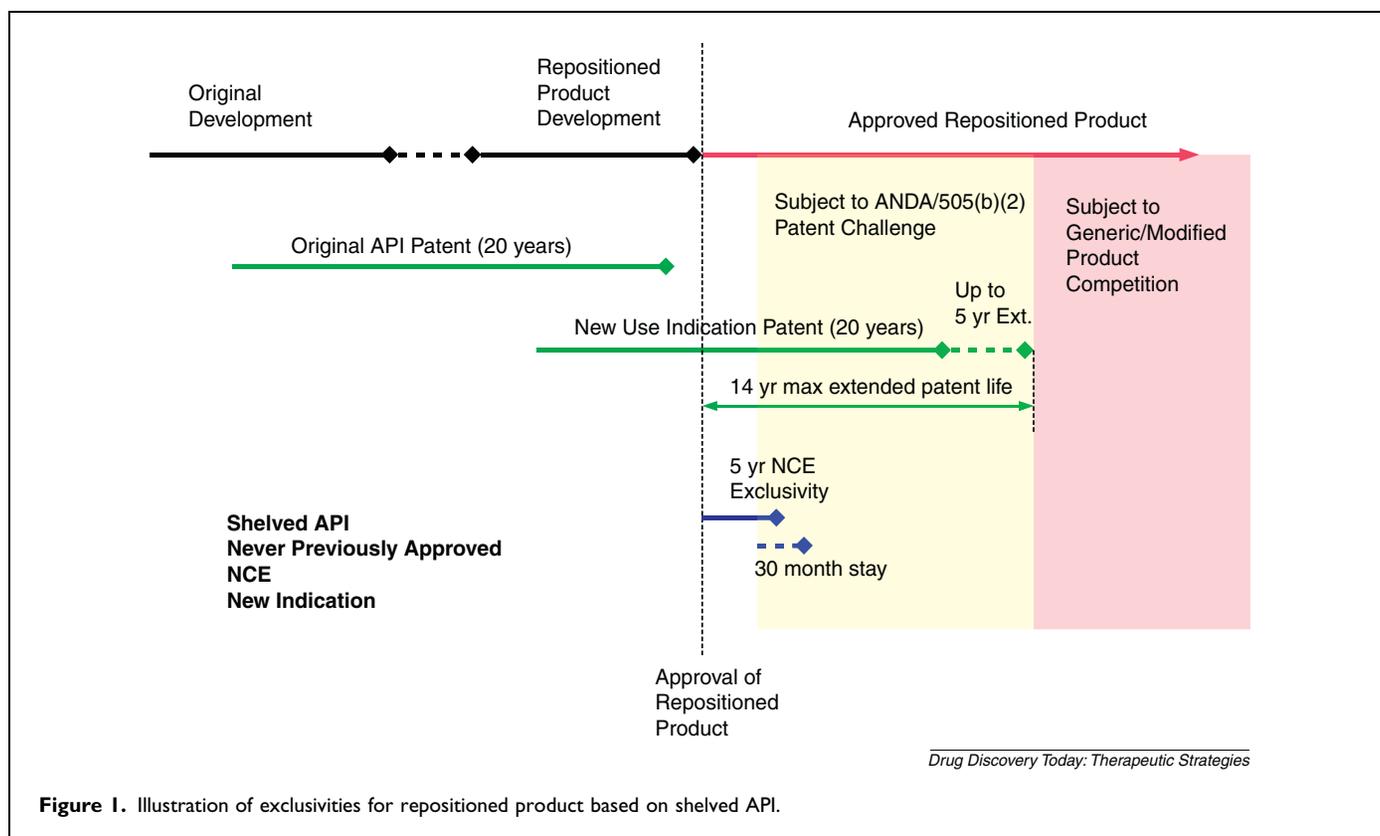
New use/formulation exclusivity is similar to NCE exclusivity but the exclusivity period is reduced from 5 years to 3 years, and there is no waiting period to file an ANDA or 505(b)(2) application. New use/formulation exclusivity will apply to a repositioned drug product that includes a significant change, such as addition of a new indication, dosage strength or form, delivery method, patient population or condition of use, but does not include a new API. Although shorter in initial duration, the new use/formulation exclusivity is also subject to the same 30 month automatic stay in the event the ANDA or 505(b)(2) application includes a Paragraph IV certification and suit is filed. However, because the application filing, and thus the patent challenge, can occur much earlier in the exclusivity period than in the case for NCE exclusivity, the resultant 30-month stay will probably have less impact on the overall length of the exclusivity period for new use/formulation exclusivity than it does for NCE exclusivity.

Orphan drug exclusivity (7 year product exclusivity) and pediatric exclusivity (additional 6 months) may also be available for the repositioned drug product in addition to the other regulatory exclusivities mentioned above.

### Types of repositioning

#### *Previously shelved API*

Previously shelved APIs can provide some of the most attractive opportunities for repositioning because under the right circumstances they can offer excellent product exclusivity and protection from generics and modified versions of the product. Figure 1 shows the exclusivities possible for a typical shelved API [6,7]. The patents covering the composition of matter for the API, original formulations and original indications were most probably filed many years earlier near the beginning of the original development effort, and will probably be near expiration or expired by the time the repositioned drug is approved. It is also probable that any patent covering the new use of the API was filed much later in the development process, that is once the new use was recognized and the API was taken down off the shelf for further development. As a result, the new use patent may have many years



**Figure 1.** Illustration of exclusivities for repositioned product based on shelved API.

of patent life left after approval. Also, because the API has never been approved before, there may be up to an additional 5 years of patent life extension available under Hatch–Waxman. It should be noted that such extended patent life cannot exceed 14 years from approval of the repositioned product by the FDA.

The newly approved product will take advantage of NCE exclusivity because the API in the product had never been previously approved nor marketed before approval for the new indication. NCE exclusivity will provide the developer with 5 years of exclusivity, including 4 years without the possibility of facing a challenge posed by a competing ANDA or 505(b)(2) application. Furthermore, an ANDA or 505(b)(2) applicant will need to challenge the new use patent with a Paragraph IV certification, and be subject to an additional 30-months stay if suit is filed.

In this case, as long as there is no pre-existing product on the market that can be used off-label for the newly patented indication, the new use patent, in combination with the ANDA or 505(b)(2) application process, can provide the developer with excellent protection for the repositioned product for a substantial period of time.

#### *New formulations and/or indications for existing marketed drugs*

New formulations of existing marketed products for the same or similar indications can also provide attractive opportunities for drug repositioning where the new formulation provides a significant clinical advantage over the original

form. Such advantage can include, for example, a sustained release formulation, a new delivery modality, dosing regime or a formulation that enhances bioavailability or patient compliance. Uniquely formulated products will probably be able to obtain composition of matter and use patents specific to the new formulation.

Repositioned products that offer no more than a new indication for one or more existing marketed drugs will probably be the most difficult to protect in the marketplace due to off-label use from readily available generic products already on the market. Furthermore, new generics may be able to enter the market by using ‘skinny labeling,’ which allows a generic product to be approved under an ANDA with only the off-patent indications on the label. It should be noted, however, that skinny labeling has come under recent attack, and may no longer provide an avenue for generic manufacturers to provide generic substitutes aimed at patented uses of the drug product.

Combining new formulations with new indications tied to those formulations may provide some of the most attractive repositioning opportunities for previously marketed drugs. These include, for example, a topical formulation of a previously systemic drug combined with a new indication suitable for topical treatment, or a new indication for the drug that requires a dosage regimen not easily replicated using existing generic products. Again, new composition of matter and use patents will probably be available for such repositioned drugs.

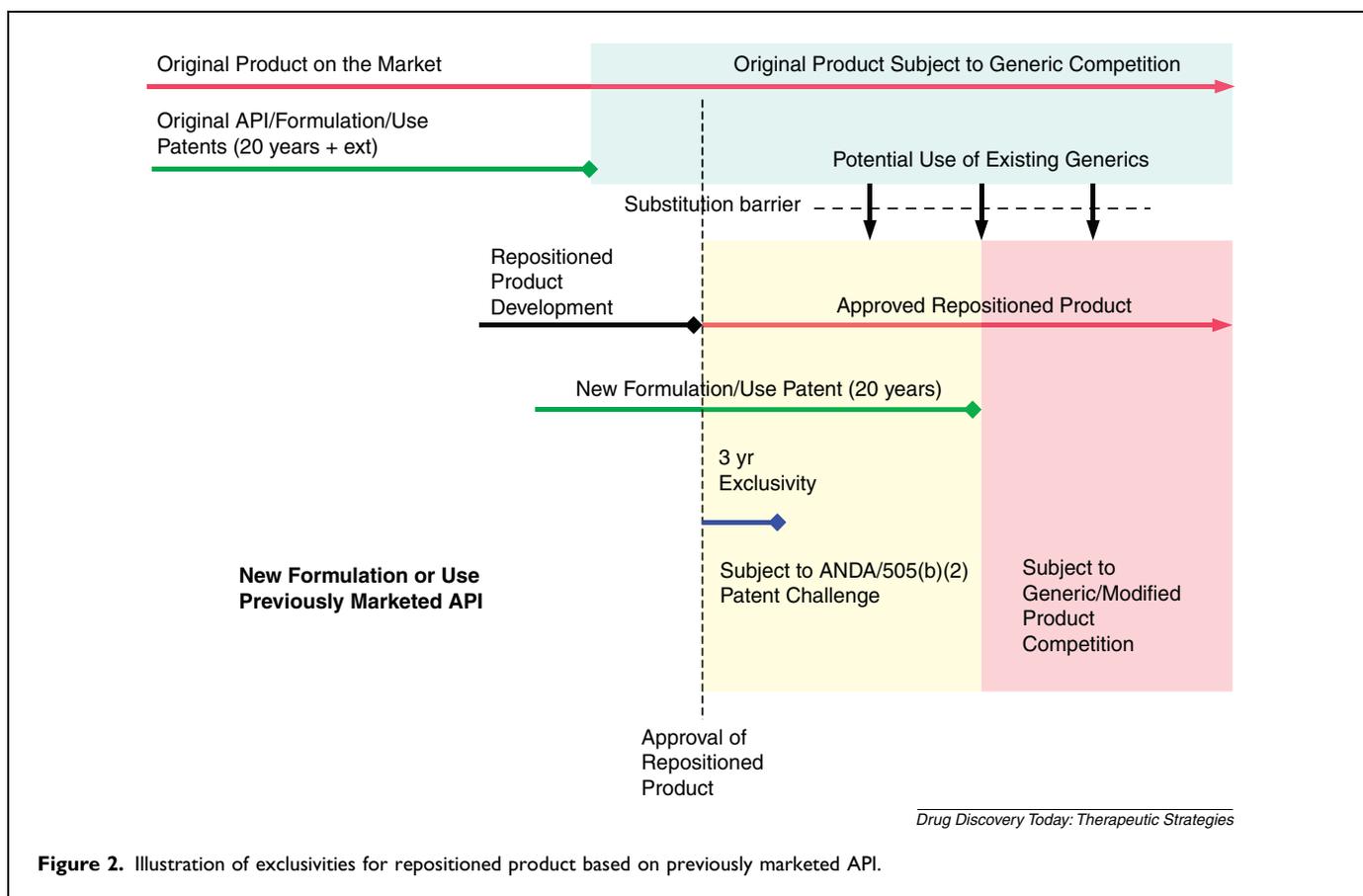


Figure 2 shows the potential exclusivities available for a repositioned drug relying on a new formulation and/or indication for an existing drug [6,7]. This example assumes that the original composition of matter patent has expired, the original product has gone generic, and new composition of matter and/or use patents are obtainable for the new formulation or indication. Here again, it is probable that the new formulation and/or indication is a recent invention suitable for patent filing late in the development process. As a result, any new composition of matter or use patent covering the formulation, or use patent covering the new indication, will have many years of patent life left after approval.

The newly formulated, previously marketed product may only take advantage of new use/formulation exclusivity because the API in the product had been previously approved before approval for the new formulation or indication. New use/formulation exclusivity will provide the developer with 3 years of exclusivity, but will be subject to a challenge posed by a competing ANDA or 505(b)(2) application at any time.

Regardless of the patent and regulatory exclusivities, success in this case will depend on an effective generic substitution barrier to prevent off-label use of the existing generic products. As long as inexpensively available generics can be prescribed in a manner that achieves the same clinical result as the more expensive repositioned product, the repositioned

product will probably fail. The best barriers include those repositioned products having a formulation required for treatment of a new indication, and where existing generics cannot be substituted for the new formulation.

### Conclusion

In selecting a drug for successful repositioning, careful consideration must be given to sources of potential competition in view of patent and regulatory exclusivity available to protect the repositioned drug product in the marketplace. The strongest and longest lived exclusivity should attach to resurrected APIs that have never been on the market, or have been recalled from the market (so no generic substitutes are available), and are being applied to new indications. Strong exclusivity may also be achievable for a repositioned drug product containing a currently marketed API through the strategic use of new composition of matter and use patents, along with a form of repositioned product and/or new use that is not susceptible to off-label use of other products containing the same API as the repositioned product.

### References

- 1 'Hatch–Waxman Act' 2011 [Public Law 98-417]
- 2 FDCA §505(b)(2); 21 USC §355(b)(2)
- 3 FDCA §505(j); 21 USC §355.(j)
- 4 FDCA §505(b)(2)(a)(iv); 21 USC §355(b)(2)(a)(iv)
- 5 FDCA §505(j)(2)(A)(vii)(IV); 21 USC §355(j)(2)(A)(vii)(IV)

- 6 Smith, R.B. (2008) Drug repositioning: selecting the right business model and partner. *CHI Drug Repositioning Summit*, October 6–7, 2008, Boston, MA, USA
- 7 Smith, R.B. (2008) Integrating intellectual property and regulatory strategies to protect repositioned drugs. *Marcus Evans Drug Repositioning and R&D Enhancement Conference*, September 18–19, 2008, Philadelphia, PA, USA
- 8 Manso, P.J. and Sokol, A.L. (2007) Life cycle management of ageing pharmaceutical assets. *Pharma. Law Insight* July/August, 16–19
- 9 Mucke, H.A.M. (2010) Drug repositioning: extracting added value from prior R&D investments. *Insight Pharma Reports* July extract of contents
- 10 Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations, U.S. Food and Drug Administration, <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>