# Life cycle management of ageing pharmaceutical assets

By Peter J Manso and Albert L Sokol.

Efforts by branded companies to repurpose or otherwise extend the business lifespan of proven drugs is yet another arena for the struggle between branded and generic drug companies.

The opportunity also attracts venture capital money, fortunately at a time when life science venture capitalists (VC) are wondering if their model is *'broken'*; early stage companies with platforms or chemical libraries that have only barely been optimised, much less tested for safety or efficacy, with huge appetites for capital and yet payback (if one is lucky) in, say, seven years.

In contrast, life cycle opportunities can permit VC-funded companies to acquire and then manage late-stage products, with fast development times, clinically validated drug-delivery platforms, experienced management, and so forth. Perhaps it is via application of a delivery platform in novel ways, improving performance or delivery of old drugs (eg better absorption or more targeted application), improving upon USP drug monograms or safety and warnings, or changing dosage forms or strengths or the number and/or times of administration. This permits VCs to balance early-stage portfolios with investments that have some late-stage attributes.

In 2008 it is estimated that US patent expiry will affect over US$80bn in global branded drug sales and that, upon generic entry into the marketplace, these branded drugs risk losing greater than 80% of market share. Simply stated: at least US$64bn in annual branded drug sales is at stake. An amount that makes both the *'branded'* pharmaceutical innovator and the generic stand up and take notice.

Over the last decade, generic companies have made serious inroads into markets created and developed by branded innovators by taking advantage of the recent changes in law most favorable to generics. While there is no doubt that tension and competition between innovators and generic companies for US market share has always been heated, intensification of this conflict in recent years owes much to these changes in legislation that allowed generics to overcome certain patent barriers, added incentives, and expedited generic approval processes.

The end result of this legislation: branded innovator companies can no longer afford to ignore generic competition or the possibility of genericisation, and must consider a *variety* of proactive and defensive strategies, well in advance of generic competition and launch. Particularly in view of the downward turn in the development of fewer blockbuster drugs, it is absolutely critical for branded companies to protect market shares of their ageing pharmaceutical assets.

Accordingly, innovator companies should consider advanced strategic planning and appropriate life cycle management to counteract this generic threat and reinvigorate ageing pharmaceutical assets. And, while successful and failed strategies populate the life cycle management landscape, success almost always requires the collaborative effort of a multi-disciplinary team approach, including research and development, marketing, business, regulatory, litigation and especially intellectual property. Moreover, using a timely integrated flexible defence of patents, litigation, commercialisation, research and development, regulatory, relaunch, business and strategic life cycle management strategies, this team must creatively assist the innovative companies in protecting their existing revenue streams by creating market barriers and sufficient market uncertainty to possibly delay or even discourage generic launch or competition.

## Developing a strategy

Typical strategies will most certainly allow for maximisation of standard exclusivity periods allotted by both the patent system and the Food and Drug Administration (FDA) market exclusivity, including patent life, patent term restoration, patent term extension, patent term adjustment, trademarking, enforcement of these IP rights through litigation and forming strategic alliances, and the independent exclusivities offered by the FDA for approval of a new chemical entity (five years), new product or indication for an existing active ingredient (three years), paediatric exclusivity (six months) and orphan drug exclusivity (seven years). *But successful strategies are always more creative.*

Experience teaches the skilled attorney(s) and their strategic teams that taking the *'next step'*, while having its risks, can also have tremendous rewards measured in dollars and cents. Some of the more obvious next steps include paediatric studies that may reap six-month regulatory patent extensions under a paediatric exclusivity (noting that multiple paediatric exclusivities may be possible for the same FDA-approved product), or developing and seeking patent protection for product line extensions, labelling matters (especially safety and warnings), dosage changes in form and strength, as well as gaining three-year regulatory data exclusivities from the FDA for new indications and drug products. In this regard, changes to the drug product, active ingredient or therapy at issue, namely, dosage strength, dosage form, dosage regimen, route or time of administration and drug delivery systems, pharmacokinetic data, metabolites, intermediates, polymorphs and isomers, in addition to formulation, bioequivalence and pharmaceutical inequivalent challenges, EPA issues, USP monograms, and safety and labelling issues, are just some tactical options available to effect life cycle extensions.

So while it is important to capitalise on the more obvious next steps, the more creative and less well-known strategies may prove significantly more valuable. Accordingly, there are numerous creative strategies that often go overlooked when considering the extension of the life cycle of an ageing drug due to a lack of true understanding as to the power of such strategies in affecting and competing

with generic entry into the market.

An understanding of life cycle management starts with a solid understanding of the FDA approval process for generics. In order to gain FDA approval, the generic drug must have the same active ingredient, strength, dosage form, safety profile, route of administration, and conditions of use as the branded or referenced product. With the exception of language protected by certain types of patents or exclusivity, the labelling of the generic drug, including directions for use, also must be the same as that for the branded or referenced drug. The experienced team will strategically make use of this information in developing a life cycle management strategy that not only adds *'value'* to the ageing asset, but will also add dollars into the accounts of the innovator company and/or any VC or other investor associated therewith. In fact, it is the opinion of these authors that the most creative strategies that utilise this mandated information often rely upon a combination of these strategies, namely, innovation and patent protection, marketing and regulatory avenues, including discontinuing and/or revising labelling to prevent generic carve-outs (otherwise known as generic skinny labelling), branded drug management and marketing, and prescription to over-the-counter (Rx-to-OTC) switching, authorised generics and defensive pricing.

## Useful examples

In our practice, we find that life cycle management strategies to preserve market share and protect branded franchises, adopted by client-innovator companies, are limited only by the knowledge and creativity of attorneys and other members assigned to the multidisciplinary team. In this respect, we provide the following six case studies, which effectively capture by example the power of successful regulatory and/or patent life cycle management strategies for ageing pharmaceutical assets.

### *(1) A regulatory strategy (capsules to tablets) to stall market erosion*

*Medicis switches patients on Dynacin capsules to Dynacin tablets long after generic market incursion*[1]

Dynacin (minocycline HCl capsules) is an oral antibiotic prescribed for acne. Since the 1990s Medicis faced direct and aggressive competition and market share erosion of its Dynacin franchise from generic minocycline capsules. In 2003, years after patent expiry, Medicis elected to switch the market from Dynacin capsules to Dynacin tablets by launching a minocycline HCl tablet. The new Dynacin tablets were not covered by patent and they apparently offered no improvement in efficacy or additional market exclusivity. Nevertheless, the new Dynacin tablets successfully stalled generic erosion for about 21 months, as depicted in Figure 1.

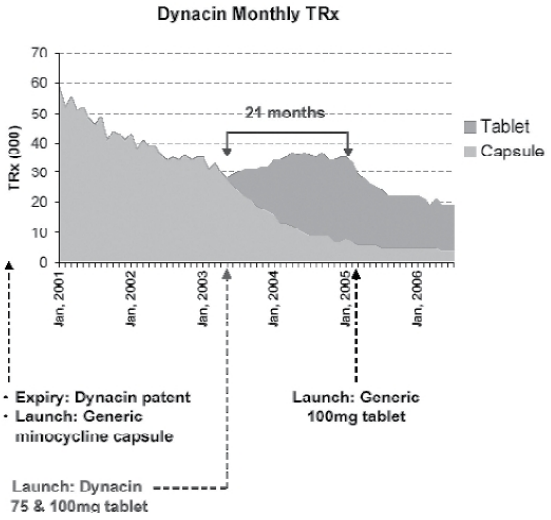



**Figure 1**

In 2001–2003 Medicis lost about 30% market share of the prescriptions written per month for Dynacin capsules to generic minocycline HCl capsules, dropping from about 60,000 Rx/month to about 30,000 Rx/month. See Figure 1. From about April 2003 to about February 2005, following the Dynacin tablet launch, Medicis was able to maintain its market share of 30,000 Rx/month, before the generic minocycline HCl tablet was launched.

In other words, Medicis was successful in stopping further generic erosion of its Dynacin franchise for about two years by adopting a regulatory strategy that involved switching dosage forms – ie switching Dynacin capsules to a new non-patented tablet formulation.

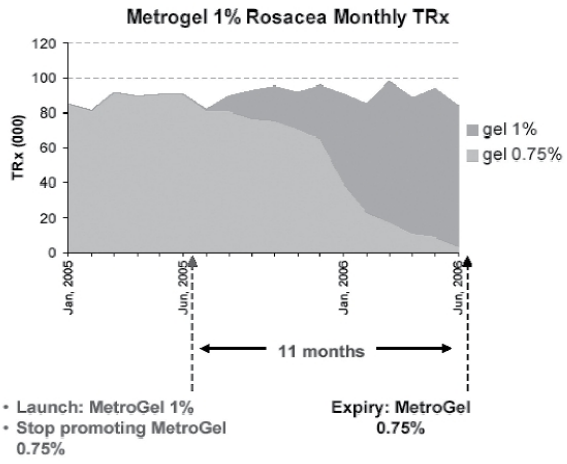
While this regulatory strategy was a short term strategy, it nevertheless temporarily stalled generic erosion and preserved market share at about 30,000 Rx/month for the Dynacin franchise for an additional 21 months, because a generic drug is not freely substitutable if it is formulated in a different dosage form from that of the innovator product. Thus, by switching to the new non-patented tablet formulation, the Dynacin franchise presented a Dynacin dosage form, different from that of the no-longer marketed Dynacin capsules, thereby creating a regulatory barrier to market erosion (by preventing the substitution of the new Dynacin tablets with generic minocycline HCl capsules), until generic minocycline HCl tablets were finally launched by Ranbaxy in about February 2005.

### *(2) A dosage strength change (0.75% to 1%) and patent strategy to convert patients before loss of market exclusivity*

*Galderma switches patients from old 0.75% MetroGel strength to new 1% MetroGel strength*[2]

MetroGel (metronidazole) is a topical antibiotic gel used to treat inflammatory rosacea. MetroGel was launched as a 0.75% gel for use twice a day and was covered by a US patent. The US patent, which covered 0.75% MetroGel, expired in June 2006.

In about August 2005, 11 months prior to loss of patent exclusivity, Galderma introduced a novel and patented 1% dose of MetroGel. See Figure 2. According to Galderma, the new 1% MetroGel strength offered improved efficacy and convenience over the 0.75% MetroGel. Moreover, the new 1% MetroGel strength provided increased drug solubility with improved stability. Before the launch of the new 1% MetroGel strength, Galderma filed for and obtained US patent no 6,881,726. The '726 patent, which covers the




The MetroGel 1% has regulatory exclusivity until June 2008 and a method-of-use patent expiring in February 2022.

**Figure 2**

new 1% MetroGel strength, is listed in the FDA Orange Book and expires on 21 February 2022. At the time of launch of the new 1% MetroGel, about 90,000 Rx/month were written for 0.75% MetroGel.

Unlike the Dynacin strategy, this strategy focuses on patent and regulatory strategies to switch patients to a new patented dosage strength prior to loss of patent exclusivity for the old dosage strength. During the 11-month transition period, prior to loss of exclusivity, Galderma stopped marketing the 0.75% MetroGel strength and converted the market to the new 1% MetroGel. From launch, the new 1% MetroGel strength has maintained robust prescription volumes for the MetroGel franchise, without market share loss, at about 90,000 Rx/month. This patent and regulatory strategy was not only successful in stopping generic erosion of market share, but it extended the life of Galderma's ageing MetroGel asset.

This Galderma strategy created patent and regulatory barriers to generic market erosion and protected Galderma's MetroGel revenue streams by preventing the substitution of the 1% MetroGel strength with generic 0.75% metronidazole gel during the three-year exclusive regulatory period and the extended patent term.

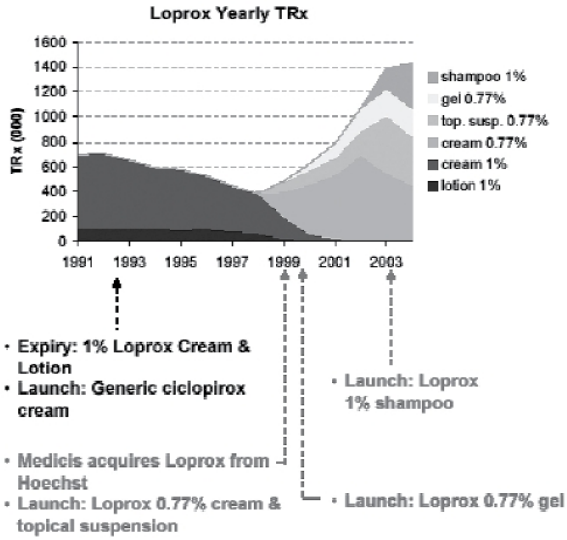



**Figure 3**

### *(3) A relaunch and patent strategy of an aged pharmaceutical asset in a genericised market to recapture market share*

*Medicis relaunches the Loprox branded franchise (new line extensions in combination with dosage form and strength changes – 1% cream to 0.77% gel) into a genericised market to recapture market share from generics*[3]

Loprox (ciclopirox) is a topical anti-fungal to treat dermatomycoces – ie ringworm and other fungal skin infections.

Before patent expiry, Hoescht marketed Loprox as a 1% topical cream and enjoyed an annual prescription volume of about 700,000 Rx/year. However, in 1999, at the time Medicis acquired Loprox, Loprox faced aggressive generic competition and significant market share erosion. In the six years following loss of patent exclusivity for the 1% Loprox cream, the annual prescription volume fell from 700,000 Rx/year to less than 200,000 Rx/year – a 72% loss of market share to generic competition. See Figure 3.

After acquiring Loprox, Medicis, through intensive reformulation, relied upon an aggressive patent and regulatory strategy to recapture Loprox market share in a highly genericised market. By relaunching novel formulations of Loprox (0.77% Loprox cream, 0.77% Loprox gel, 0.77% Loprox suspension and 1% Loprox shampoo), Medicis doubled the total annual prescription volume achieved prior to loss of exclusivity – ie 700,000 Rx/year to about 1,400,000 Rx/year.

This Loprox case study shows that a patent-regulatory-based relaunch strategy, even in a highly genericised market, may not only achieve but surpass prior sales, even years after generic competition.

### *(4) An Rx-to-Rx and Rx-to-OTC switch and patent strategy*

AstraZeneca switches patients on Rx Prilosec to Rx Nexium and switches Rx Prilosec to OTC Prilosec before loss of exclusivity[4]

AstraZeneca, well in advance of generic launch and loss of patent exclusivity, employed a different strategy by switching patients from its blockbuster drug Prilosec (omeprazole), to a next-generation line extension, Nexium (esomeprazole), and by switching Rx Prilosec to OTC Prilosec. According to AstraZeneca, esomeprazole, one of the two stereo-enantiomers in omeprazole, has a higher degree of bioavailability than

Prilosec. In making this Rx market switch, not only did AstraZeneca retain market share, but AstraZeneca actually increased sales for this gastrointestinal franchise by about US$500m. To underscore the value of this life cycle management strategy, AstraZeneca grew annual revenues for its proton pump inhibitor franchise by about US$500m in one year.

### *(5) A launch and patent strategy of line extensions to stall erosion of market share of an ageing pharmaceutical asset*

*Bristol-Myers Squibb switches patients on Glucophage to Glucophage XR and Glucovance*[5]

In late 2000 and early 2001 Bristol-Myers Squibb (BMS) launched two line extensions – Glucophage XR, an extended release formulation, and Glucovance, a combination of Glucophage with glyburide – to replace its blockbuster drug Glucophage, an oral anti-diabetic medication used to treat type 2 (non insulin-dependent) diabetes.

Sales of Glucophage apparently peaked in about 2001 at approximately US$1.8bn. In 2002 generic competition reduced BMS's revenue streams for Glucophage to about US$246m, a loss of about 84% market share. By June 2001, however, the two line extensions had earned about US$778m and, by 2003, the Glucophage XR and Glucovance franchises earned an additional US$1bn. At the end of 2003 Glucophage XR began to face generic competition and market share erosion. While the loss of market share for the Glucophage franchise was quite dramatic, the life cycle management strategy to populate with Glucovance and Glucophage XR line extensions generated an additional US$1bn in revenue for an additional two years.

### *(6) An R&D and patent strategy to reintroduce a very old genericised drug*

*Niacin (nicotinic acid) is reintroduced as Niaspan to treat abnormal cholesterol levels once a day at night*

Since about the mid 1950s, it has been known that niacin (nicotinic acid) has lipid-altering properties, and that it is quite effective in raising high-density lipoprotein cholesterol while decreasing both triglycerides and low-density lipoprotein cholesterol. Uses of immediate-release formulations of niacin administered three times a day to treat abnormal cholesterol levels were limited by cutaneous flushing. In an effort to overcome this problem, the pharmaceutical industry resorted to twice-daily extended-release niacin formulations to change niacin absorption rates to reduce or mitigate the flushing side effect commonly associated with niacin use. Unfortunately, uses of these twice-a-day extended release niacin formulations were also limited due to an increase in the risk of hepatotoxicity.

In 1997, approximately 40 years later, the FDA approved Niaspan to treat abnormal cholesterol levels. Niaspan, which was developed by Kos Pharmaceuticals Inc, is an extended-release formulation of niacin.[6] Unlike previous extended release niacin formulations, Niaspan is used once a day at night, not twice daily, to treat cholesterol, without an increase in risk of hepatotoxicity.

In about six years following launch, Niaspan had achieved reported annual sales of about US$211m.[7] By 2005 Niaspan was reported to have reached about US$405m in annual sales.[8] In about December 2006, Abbott Laboratories Inc acquired Kos Pharmaceuticals Inc for cash of approximately US$3.8bn, net of cash held by Kos Pharmaceuticals Inc, to become a leader in the field of dyslipidaemia and cholesterol management.[9]

## Conclusion

Innovative companies can successfully rejuvenate ageing pharmaceutical assets to counteract generic threats and to preserve market share and income streams, when appropriate strategic planning and life cycle management are implemented, preferably in advance of generic launch, but even after genericisation under certain circumstances. Such future successes can be accomplished through a variety of proactive and defensive strategies – eg patent, regulatory, research and development, and marketing strategies, coordinated and planned well in advance of or even after generic competition or launch. It is the complimentary and coordinated use of these strategies that can inject a breath of new life into all but written-off aged pharmaceutical assets.

In our practice, we meet with in-house life cycle management team members on a regular and consistent basis to maximise our understanding of the technology, competitive landscape and regulatory and marketing issues relating to each of the pharmaceutical assets, so that we can best plan, create and maximise patent, regulatory and enforcement strategies that will create and maintain maximum market value even in the face of aggressive generic competition. Such close communication is also essential to ensure that life cycle management strategies are consistent with the innovator companies' overarching regulatory, research and development, commercial and business strategies. ■

1 Case Study and Figure 1, Waseem Noor and William Leaf-Herrmann, Principals, SDG Life Sciences, a Unit of IMS.
2 Case Study and Figure 2, Waseem Noor and William Leaf-Herrmann, Principals, SDG Life Sciences, a Unit of IMS.
3 Case Study and Figure 3, Waseem Noor and William Leaf-Herrmann, Principals, SDG Life Sciences, a Unit of IMS.
4 See *'Branded Drugs Gain New Hope in Battle against Generics'*, *Pharma Industry News*, 11 August 2005. See also *Cutting Edge Information* at: *www.pharmagenerics.com*
5 See *Cutting Edge Information* at: *www.pharmagenerics.com*
6 Abourjaily, H M, *'A Review of Niaspan, an Extended-Release Niacin Nutrition in Clinical Care'*, 4(5): 250–255 (2001).
7 Pomona, N Y, June 16 /PRNewswire-FirstCall/ – Barr Laboratories, Inc.
8 News Release: The Health Care Sales and Marketing Network. Barr Receives Final FDA Approval for Generic Niaspan(R) Extended-Release Tablets (April 27, 2005).
9 Abbott Annual Report 2006, Note 11 – Business Combinations, Technology Acquisitions and Related Transactions.

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