SAVE YOUR BRAND THROUGH REFORMULATION

How creative life-cycle management can protect your bottom line

By Nelly Edmondson

Drug reformulation can be a successful — and profitable — way to extend the life of brand-name pharmaceutical products. Reformulated drugs that better meet patients' clinical needs or reduce side effects and/or toxicity, for example, often achieve success in the marketplace. So can reformulations that significantly enhance efficacy and compliance or preserve efficacy while lowering drug dosages.

Reformulation is especially important now, thanks to the much-discussed "patent cliff," a metaphor for what occurs when established drugs go off patent, leading to potentially steep drops in revenue. Indeed, the patent cliff is "one of the biggest drivers of reformulation," said Anil Kane, PhD, MBA, Executive Director and Global Head of Formulation Sciences Pharmaceutical Development Services at Patheon, Inc. "Loss of patents means huge business losses, unless the brand-name drugs are substituted with other drugs in the pipeline or are reformulated."

Reformulation 101

When considering reformulation strategies, companies sometimes utilize "older drugs that can be delivered in new ways," noted Charles Grudzinskas, PhD, founder of NDA Partners, a global strategy consulting firm specializing in expert product development. Transdermal patches, intranasal and sublingual options, as well as dissolvable film strips, are all finding acceptance from physicians and patients. Some companies are even making it a priority to design patient-friendly delivery systems for people who are unable or unwilling to undergo injections, or who have difficulty swallowing. (See sidebar, "An easier way to deliver.")

Other popular reformulation strategies include developing pediatric line extensions and controlled-release formulations. Although pediatric products command a smaller market segment than products for adults, producing them often makes sense from a regulatory and market perspective, because launching a pediatric version of a drug can get a company a six-month patent extension, thereby delaying the entry of competitive products into the market. Companies can take the same approach with controlled-release formulations, which sometimes offer compliance benefits or a better side effects profile than the original version.

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Another strategy being looked at is different dosage strengths. Newer technologies can allow manufacturers to lower dosage strength while showing similar or better clinical efficacy, and/or fewer side effects. "These technologies may not have been explored when the drug was first looked at," Dr. Kane said. Reformulation can be an opportunity "to revisit" the issue, and has been used — or is being considered — for a variety of indications. An obvious case in point is so-called "low dose" oral contraceptives, which are as effective as their higher-dose forerunners but are associated with a lower risk of stroke, heart attack and other serious side effects. Indeed, clinical practice has shifted from reserving low-dose OCs for specific patient populations to using them as first-line therapy.

Creative combinations

To create favorable synergistic clinical effects, savvy reformulators are also developing novel drug combinations. For example, several years ago, Bristol-Myers Squibb Co. and AstraZeneca teamed up to create Kombiglyze XR to improve glycemic control in adults with type 2 diabetes. The once-daily tablet contains saxagliptin and extended-release (XR) Metformin. The U.S. Food and Drug Administration (FDA) approved Kombiglyze XR in 2010. Metformin has also been combined with Actos, Avandia, glimepiride, Januvia, and Prandin, among others.

Combination drugs are also being used in other therapeutic areas, such as cardiovascular disease, women's health – including oral contraceptives and hormone replacement therapy – and HIV infection. "Fixed dose combos are on the rise," Dr. Kane said. "There have been lots of good data in the past 10 years, and we have seen tremendous growth in FDA approvals of fixed-dose combinations."

In the HIV area, three and even four drugs are being combined to produce one-pill-a-day treatment regimens: In July 2006, the FDA approved Atripla, a single-tablet regimen for HIV that combines efavirenz, emtricitabine, and tenofovir disoproxil fumarate, which is manufactured by Gilead Sciences. In 2012, the FDA approved Gilead's Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate), a once-a-day combination pill designed to treat HIV-1 in adults who have never before been treated for HIV infection.

Making old drugs new again

Dr. Kane, whose company is currently working with some 300 clients, describes yet another reformulation technique. "We see a number of existing molecules being used for completely *new* indications," he said. Since these existing molecules are generic and can be utilized by any group, the drugs being used for new indi-

cations may not have been discovered or manufactured by the same sponsor that is developing the reformulated drugs.

As a case in point, Tonix Pharmaceuticals in New York City is in the process of developing new treatments for challenging chronic pain disorders of the central nervous system (CNS), including two diagnoses that have been very much in the news lately: fibromyalgia and post-traumatic stress disorder (PTSD). To do this, the company is using new formulations of the FDA-approved generic muscle relaxant cyclobenzaprine. Other companies currently market cyclobenzaprine, which works by blocking nerve impulses sent to the brain.

"We tried a number of reformulation strategies," explained Seth Lederman, MD, the company's Co-founder, CEO and Chairman. Eventually, Tonix came up with a sublingual tablet that is taken once daily at bedtime. Designed to disintegrate under the tongue and to cross sub-mucosal membranes, Dr. Lederman says it achieves "faster absorption and faster uptake into the brain" than other forms of cyclobenzaprine.

Dr. Lederman adds that this treatment is non-addictive, and that the once-daily dosing schedule will help patients with long-term compliance. "Our product is a new class of medication that targets sleep quality," he said, noting that patients with fibromyalgia and PTSD often have difficulty getting enough sleep. "By having patients take the medication at bedtime, you are also helping them establish a nighttime ritual -- good sleep hygiene – that will help them plan their day and then sleep for a reasonable period of time."

If all goes well, Tonix is hoping for FDA approval for both indications in 2017. "The area we are working in is one that big pharmaceutical companies don't want to get involved in," Dr. Lederman said, "because chronic pain patients often have suicidal thoughts. What we're doing for chronic pain is, arguably, comparable to what Gilead did for AIDS." Many big pharma companies, he added, thought AIDS was too controversial — so they let Gilead have the entire field. "Since then, Gilead has taken an intractable problem and made substantial improvements in treatment."

No matter which reformulation strategy is chosen, timing is key. According to formulation expert Dave Savello, Ph.D., a scientist at NDA Partners, it is important for manufacturers to launch a new formulation well in advance of patent loss to allow physicians time to switch. "Although every drug and every marketplace are different," he continued, "you really have to take a reformulated product out there at least a year or two before patent loss, because converting physicians and patients is going to take time."

Speed to market

In the past, pharmaceutical companies that discovered new molecules often developed many formulations and dosage points upfront. Diclofenac is a nonsteroidal anti-inflammatory drug (NSAID) taken or applied to reduce inflammation and as a pain-reduction therapy for certain conditions. Originally developed by Ciba-Geigy (now Novartis) in 1973, diclofenac was first approved for use in the United States in 2007, and is now supplied as, or contained in, medications under a variety of trade names. When it was first discovered, Ciba-Geigy developed a sodium salt, a potassium salt, an enteric-coated tablet, an extended-release capsule, and a powdered form to be mixed with water.

Today, fewer companies are introducing multiple formulations and dosages upfront. "Now, speed to market is very much the priority," Dr. Kane said. "Companies want to take a product to market, launch the product, generate revenues and, in parallel, look for other routes of administration."

Making money quickly is key, he said, because the financial investment required to bring a molecule to market is higher than ever, and competition and pressures are rising. Companies do look at different dosages and forms of administration to delay generic competition, Dr. Kane added, "but at a later stage as a lifecycle management strategy."

Challenges ahead

None of this means that successful reformulation is easy. Pharmaceutical companies attempting to reformulate their products face stiff challenges in today's difficult sales environment. Healthcare payers, focused on cost cutting, are becoming increasingly reluctant to pay for reformulated medications that aren't demonstrably superior clinically – and just as cost-effective – as existing options. And they demand hard, real-world outcomes data to back any claims about a reformulated medicine's supposed advantages. "Payers are becoming very touchy," Dr. Savello said. "Because of costs, many big pharma companies are relying on specialty pharma to take the risk of reformulating old drugs."

Also adding to the mix is a rapidly changing healthcare landscape, declining R&D productivity, and fierce competition from generics, all of which are "conspiring to produce lower growth and slimmer profit margins for the pharmaceutical industry," Dr. Savello added.

In fact, a recent study by IMS Health estimated that between 2011 and the end of 2015, drugs falling off the patent cliff will have cost pharmaceutical manufacturers $120 billion in lost sales.

Never too soon

Perhaps the most important thing pharmaceutical manufacturers can do to safeguard the bottom line is to review the reformulation possibilities and challenges early in a brand's life cycle, and then decide which approach is best for each specific product. "There is no one answer," Dr. Kane concluded. "With different drug candidates, different approaches can be successful. It depends on the drug candidate and its properties."