GENERICS COMPANIES SEEK NEW REVENUE STREAMS

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THE GLOBAL 505(B)(2) EXPERTS
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THE 505(B)(2) APPROVAL PATHWAY PROVIDES OPPORTUNITIES FOR GENERICS COMPANIES SEEKING NEW REVENUE STREAMS

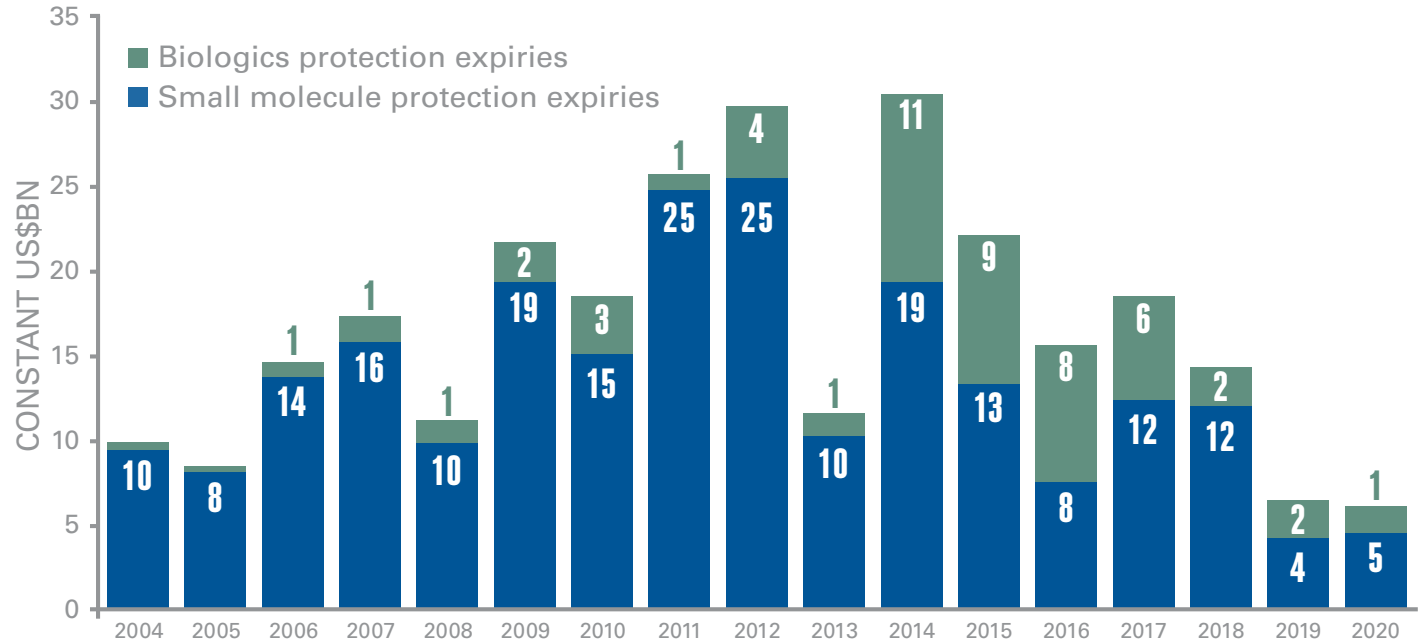
INTRODUCTION

The "cliff" has passed for pharma but has just begun for generics companies that have benefited from the high number of drugs going off patent. CEOs of generics companies report solutions to bridge the revenue gap are limited. Perhaps the most attractive option among those is the U.S. Food and Drug Administration's (FDA) 505(b)(2) approval pathway, which can offer faster approval, reduced development costs, lower risk and, in certain cases, market exclusivity. In this white paper, readers will gain insight into why developers are choosing 505(b)(2), how products are identified and models for development.

A LOOK AT THE GENERICS LANDSCAPE

Current market analysis predicts a precipitous drop in patent expirations for small molecule drugs over the next few years. The so-called "patent cliff" is over for pharma but has only just begun for generics companies that have benefited from the large number of drugs going off patent in recent years (**Figure 1**). As the number of drugs coming off patent declines, generics companies must seek new revenue sources. Recent trends in the pharma industry suggest that large pharma companies are focusing R&D efforts on the development of new biological medicines. Unfortunately, unlike small molecules, biologics are

VALUE OF PRODUCTS AT RISK 2004-2020



Source: IMS Health, MIDAS, Market Segmentation, Jun 2010

Figure 1

difficult to reproduce due to the complex techniques involved in their manufacture and validation. In addition, regulatory approval of copied biological medicines, known as biosimilars, is conducted through unique European Medicines Agency (EMA) or processes with more requirements than small molecule generics.

Neal Hansen, managing director of Hansen Strategy, an independent consulting firm specializing in life cycle management and branding strategy in the pharmaceutical industry, sees the generic patent cliff as a two-fold challenge for generics companies. First, as the volume of drugs coming off patent protection decreases, the massive growth of the generics market provided by duplication of blockbuster drugs and adoption of generics by consumers is slowing. Second, as the pipeline slows, competition within markets increases. Generics giant Teva Pharmaceuticals' decision not to launch its generics version of Lipitor was, in part, driven by the emergence of eight other companies offering competing products. According to Hansen, generics companies are taking two approaches to overcome these challenges. First, they are working to identify and develop hard-to-make or hard-to-copy generics that will discourage some companies from getting into the market and, second, they are engineering barriers to competition, such as the longer exclusivity possible through the FDA's 505(b)(2) approval process.

CEOs of generics companies have a limited number of solutions to bridge the revenue gap in light of the looming generic cliff. These include counting on economies of scale to keep ahead of competitors, branding their own products, specializing in hard-to-make products, making large acquisitions and/or developing drugs through the FDA's 505(b)(2) pathway or the equivalent European hybrid process.

Determining the marketability of a new product is an important consideration in these decisions. Many generics companies are finding it a challenge to identify the pathway that makes financial sense for

Table 1. Comparison of 505(b)(1), 505(b)(2) and 505(j) pathways

	505(b)(1)	505(b)(2)	505(j)/ANDA
Nonclinical/Toxicology data	Usually required	Not always needed	Not required
Clinical trial	Usually required	Not always needed	Not required
Exclusivity	3 or 5 years	3 or 5 years	180 days
Timing	8-15 years	2-5 years	1-2 years
Costs	$500m-$2b	$3m-$7m	$50k-$750k

Data from Duggal, 2014 [2] and FDA [3]

Table 2. Types of applications allowed under 505(b)(2)

Modification	Examples
Route of administration	Intravenous to oral administration
Change in active ingredient	Different salt, racemate, enantiomer
Dosage form	Oral to transdermal patch
Strength	Lower or higher strength
Combinations	Change one ingredient in previously approved combination or new combination of previously approved drugs
Formulation	Different quality or quantity of excipient, does not fit 505(j)
Dosing regimen	Change from twice daily to once daily
New molecular entity	Prodrug of a previously approved drug
Indication	Expansion of diseases drug is approved for
OTC	A previously approved drug switched to OTC or change in an existing OTC drug
Naturally derived or recombinant product	New form of approved drug from new manufacturing source (not biologics)
Bioinequivalence	Controlled-release version of a drug

OTC = over the counter. (Data from FDA guidance, Applications Covered by Section 505(b)(2), 1999 [3])

their business. In particular, companies may seek assistance from third-party consultants to determine whether there is a need and a profitable market for a meaningful improvement on a mature product that is within their manufacturing capabilities. Similarly, commercialization of a generic involves deciding whether to market it as an unbranded generic, a generic that incorporates the company's name in the product's name or a branded generic with its own new brand name. There are good reasons for choosing to go with a branded generic product, but companies must evaluate whether they have the infrastructure to handle commercialization and promotion of this type. While the decision regarding which avenue to pursue will depend on each company's unique situation, there are compelling reasons for generics companies to consider 505(b)(2) drug development.

WHY 505(B)(2)?

The current landscape suggests that generics companies that move toward development of 505(b)(2) products can enjoy some immediate benefits in terms of regulatory requirements. This is because, although they are considered to be a full new drug application (NDA), 505(b)(2) filings can be accompanied by existing data from outside sources. This means they are less expensive than traditional 505(b)(1) NDAs and have lower risk for generics companies with limited research and clinical trial resources (**Table 1**). In fact, the rate of success in Phase III trials of 505(b)(2) products is 66% compared to 41% for 505(b)(1) products.[1] Also, because 505(b)(2) filings may require essential clinical data, there is the potential for three to five years of patent exclusivity (compared to 180 days for first to file with 505(j)/generics/abbreviated NDAs) depending on the amount of essential new data required. Finally, although the FDA has recently promised to improve review times for ANDA (505(j)) filings, the current median approval time is 26 months. The approval process is also backlogged by 36–42 months and will take some time to improve.[4] By contrast, there is no backlog for 505(b)(2) filings and, thus, their review is accelerated. The mean time for approval of all 505(b)(2) applications approved since 2003 is just over 12 months.

Many generics companies seek to separate themselves from competitors by developing niche market products. 505(b)(2) applications provide a pathway for carving out niche markets because there are many different options for specialization (**Table 2**). Investments in development of a specific delivery system, for example, can be applied to a number of different drugs, lowering costs for

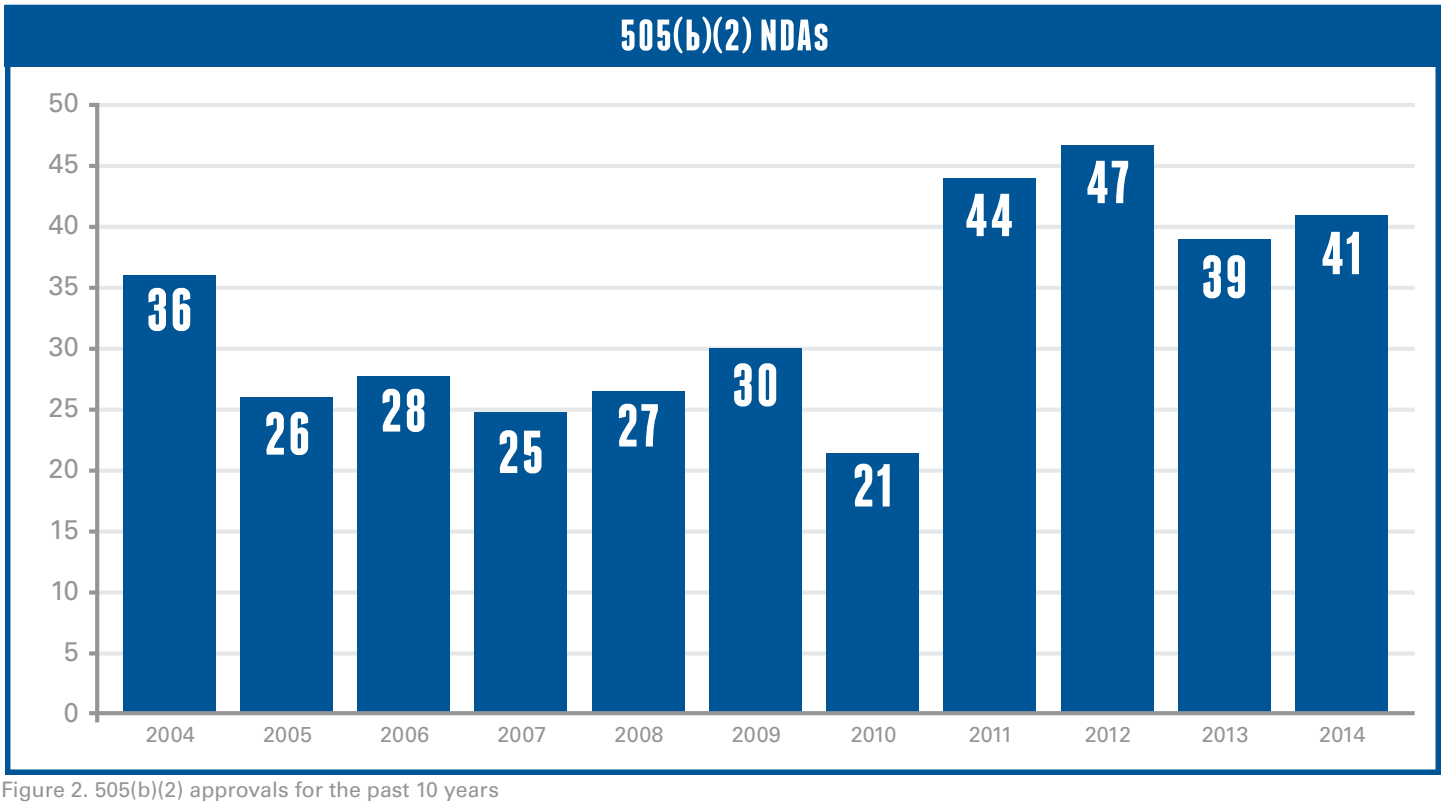


Figure 2. 505(b)(2) approvals for the past 10 years

each subsequent drug modification. Lower costs for development of niche products and their approval provide improved ROI for 505(b)(2) drugs compared to many generics.

A LOOK AT THE 505(B)(2) LANDSCAPE

What are the recent trends in approvals for 505(b)(2) products? Analysts believe that 505(b)(2) development is more than just a regulatory pathway: It is a competitive strategy that can lead to product approval with lower risk, reduced development costs and faster speed to market than generics. Generics companies appear to be getting the message. From 2010 to 2013, 43% of all NDAs approved have been 505(b)(2) drugs.[6] In 2014, this number was 50%, with 41 new 505(b)(2) drugs approved compared to the same number of new molecular entities (NMEs)[7,8] (**Figure 2**). This percentage is expected to rise to more than 80% over the next few years.[9]

New dosage forms (38%) and new formulations or manufacturing techniques (31%) were the most common types of approved 505(b)(2) products between 2010 and 2013 but approvals were also sought and received for new combinations, new molecular entities, new indications and OTC versions.[6] This trend has continued with new formulations or manufacturing techniques comprising 41.5% of approvals, new dosage forms accounting for 31.7% of approvals, and new combinations comprising 14.6% of 505(b)(2) approvals in 2014.[8] Teva had five drugs approved through 505(b)(2) between 2010-2013 including Adasuve, an inhaled form of the oral anti-psychotic drug loxapine, and has as many as 14 other drugs in the 505(b)(2) pipeline.[6,10] However, 2014 numbers show diverse and substantial competition in this area with no single company having more than two 505(b)(2) approvals.[8]

South Korean pharmaceutical company Hanmi is partnering with Amneal Pharmaceuticals in the U.S. to market a new delayed-release version of Nexium approved through the 505(b)(2) pathway.[11] Hanmi and Amneal will aggressively market the new product, Esomezol, which is a strontium-salt version of the active ingredient, esomeprazole magnesium, to take advantage of the remaining patent protection for Nexium. The FDA is still determining whether it will grant patent exclusivity to Hanmi under 505(b)(2).[11]

HOW ARE DEVELOPERS DETERMINING THAT 505(B)(2) IS THE SOLUTION?

For large pharmaceutical companies, opportunities for new pharmaceutical products exist through life cycle management strategies within the products, patents, technologies and intellectual properties they already own or control. This may not leave much on the table for generics companies that must make their selection of 505(b)(2) candidates carefully based upon their own manufacturing and therapeutic capabilities and their marketing strategy. These decisions may be driven by R&D teams that may discover a new indication or new formulation for an existing drug. Alternatively, 505(b)(2) strategy decisions may be driven by marketing factors. In these cases, new opportunities may arise through market feasibility studies that identify emerging niches. Beyond identifying candidates, there is significant challenge in assessing candidate feasibility.

Consider the following:

- **Scientific Viability:** Does the science make sense? For instance, is the formulation or chemistry practically and pragmatically achievable? Is it scalable? Are API ingredients available and affordable?
- **Medical Viability:** Does the product have a clear niche in the medical specialty? Is it effective for solving a unique problem or solving a problem in a unique way? Does it present an acceptable risk/benefit? Is it appealing to the proposed patient population?
- **Regulatory Viability:** What clinical trials or other data will be required to gain approval? Can development be expedited? What distinguishing information can be presented on the labeling for eventual promotional activity?
- **Commercial Viability:** Is there a viable market for the product? What is the potential for future competition or substitution? What is needed to ensure reimbursement? What is the optimal pricing?

To answer these questions and others, many companies enlist third-party consultants or global strategists to identify, evaluate and select the most viable development opportunities. Indeed, this approach is beneficial to

establish triage criteria for development pipelines/ portfolios and is a sensible first step in creating a comprehensive development strategy.

HOW ARE DEVELOPERS EXECUTING 505(B)(2) DEVELOPMENT?

Depending on their in-house capabilities, generics companies may need assistance in sourcing the product, developing the product or commercializing the product. There are a number of models to choose from for strategic planning and execution of a 505(b)(2) development plan.

Product Identification

- **In-house:** Company identifies product in-house and develops product in-house based on R&D capabilities.
- **Acquisition:** Generics company acquires another company that provides new potential products in the therapeutic area of interest and develops these with existing in-house expertise.

Development

- **Partnership:** Generics companies may partner with a product development organization. The product development organization is owned by an outsourced development service provider or contract research organization (CRO). A separate entity may be established for this partnership. The generics company contracts with the entity and part of the agreement is that the outsourced service provider is used to develop the product. With this agreement, both parties have an invested ownership in the product being developed. The generics company ideally ends up with a successfully licensed product.
- **Acquisition:** Company identifies a market opportunity in-house and acquires a company with the expertise to develop the product.
- **In-house/outsource combination:** Company identifies a product in-house and development is outsourced.
- **Completely outsourced:** Company outsources identification and development.

Commercialization

- **Licensed:** Company is approached or approaches a manufacturer about a new product.

It has been suggested that generics companies are more likely to use acquisition as a means of gaining needed capabilities than they are to form partnerships. Recent activities by the top three generics companies support this idea. In the past several years, Activis (formerly Watson) has expanded its reach in women's health, dermatology, gastroenterology and urology through purchase of Uteron, Warner Chilcott, Forest, Durata and Allergan. While much of this flurry of acquisition will bring Activis revenue from mature assets, it also positions Activis to develop specialty products with unique drug delivery systems and hard-to-copy generics that could be approved through 505(b)(2). Teva is reportedly focusing its core growth strategy on the development of new therapeutic entities that combine or reformulate existing drugs or are administered through the use of new delivery systems, and Teva has acquired companies with established global markets to complement its considerable manufacturing capability.[12]

Similarly, Mylan's acquisition of Abbott doubles its marketing infrastructure in Europe and expands its specialty generics capabilities. Mylan's recent acquisition of some of India's FamyCare women's health business complements partnerships the two companies have in other markets and also the specialty generics provided by the Abbott acquisition. Smaller generics companies without large acquisition resources may seek to expand their product identification, development and commercialization capabilities through partnerships and outsourcing.

Working with in-house development teams or the right partners, generics companies can find new revenue sources through development of 505(b)(2) products. A recent review from BioPlan Associates on trends in biopharmaceutical manufacturing found that companies are no longer using outsourcing as a cost-saving measure but are viewing these partnerships as a strategic move toward improved quality and value.[13] While the strategy to develop products via the 505(b)(2) pathway presents, perhaps, a greater opportunity than ever for many generics developers, the way those companies go about identifying the right opportunities — the strategy behind the strategy, if you will — is where the most value can be added to the process.

About the author

Ken Phelps applied more than three decades of industry experience to found Camargo Pharmaceutical Services in 2003. As an expert in drug development and the industry authority on 505(b)(2) drug development, Ken leads a team that has guided more than 200 FDA approvals and has the largest percentage of 505(b)(2) submissions of any team submitting to the FDA. Camargo hosts numerous seminars and forums advising on the opportunities 505(b)(2) presents for global companies and routinely presents on the financial challenges caused by the generic cliff — visit blog.camargopharma.com, where Ken and his team discuss current market trends.

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