
Global generics profitability: Increasing need for business development and licensing

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Abstract This paper examines key success factors for global and regional generics companies, including the ability to license in or acquire products. It explores the importance of business development deals to secure early, exclusive access to active pharmaceutical ingredients for patent challenges, as well as more profitable dose-form products that fuel growth. Further explanation of consolidation among global generics companies, and the limited number of independent, high-calibre active pharmaceutical ingredient manufacturers to support these companies, is provided.

Keywords: *business development, licensing, M&A, API, portfolio selection, generics profitability, India, China, Europe, USA*

INTRODUCTION

In the global generics industry, complex portfolio selection processes have become crucial to obtain products that will be profitable and to drive growth. The successful portfolio selection process is underpinned by global business development and licensing to license in or acquire products and active pharmaceutical ingredients (APIs) for the core products.

OLD VERSUS NEW MODELS

The old generics business model involved using IMS data to find blockbuster products and evaluate when their product patents expired. This simplistic product selection model has been jettisoned at leading generics companies, which now use sophisticated models to generate and analyse lists of product opportunities based on complex criteria. The criteria for product selection

include: product characteristics and fit; technical and regulatory issues; sales value and forecast; estimated competitiveness; manufacturing requirements; API supply; brand company defence tactics; and patents and exclusivities. Patents are evaluated for weaknesses that can be challenged or circumvented, as well as for estimated expiry dates. Investigation of the commercial potential and fit of product candidates extends to competitive analysis of the number, competitive strength, sourcing and pricing behaviour of likely generics competitors, as well as to evaluation of the API suppliers on both technical and business criteria. Sophisticated generics companies extend their models to prediction of likely partnerships between strong API suppliers and generics competitors, as well as to the timing of generics company and competitor market entry and exit.

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BLOCKBUSTERS LIMIT PROFITS

For blockbuster solid, oral dose-form drugs, generics competition is assumed to be intense. Without an exclusivity period based on first-to-file (FTF) status and a successful patent challenge — or other factors limiting competition such as API availability or patents — the blockbuster oral drugs are unlikely to be profitable for multiple players in the highly generics-orientated European markets or the USA unless the generics company is backward integrated into API production.

For the largest generics companies, while there may be a requirement to sell the blockbuster products, without attractive profits during an exclusive or semi-exclusive marketing period, and absent an especially competitive internal API cost advantage, the oral blockbusters are unlikely to be attractive contributors to generics companies' bottom lines. Therefore, generics companies must win an exclusive or semi-exclusive launch in a blockbuster product, or backward integrate into API manufacture. More importantly, generics companies must successfully launch other types of products that are more profitable to fuel growth and profitability.

Some generics companies that are not backward integrated into API production believe that the big-selling oral solid-dose products that lack barriers to entry are best left to vertically integrated generics companies or to Indian or other overseas companies that have lower costs and will probably accept lower margins, and licensed in as dose-form products. Some generics companies may accept or even seek lower margin products. The impact of these companies on the marketplace is a subject for later inquiry.

FINDING PROFITABLE PRODUCTS

Far more interesting to generic business development efforts than commodity

blockbusters, however, is the challenge of managing the portfolio selection process to find profitable, specialised, product opportunities. Attractive products may be developed internally or licensed in, perhaps through a business development deal to gain exclusive access to an advantageous or early API source. Specialised, profitable product opportunities include many different types of product opportunities and are not limited to that of being FTF and successfully challenging a patent.

APIs ARE CRUCIAL

Generics companies in both Europe and the USA have traditionally purchased their APIs, following a different business model to that of the traditional, big pharma model of producing the API, at least the final synthetic steps, internally. Teva, Sandoz and several of the leading Indian companies are leaders in changing the generics business model. Teva has substantial capabilities in developing APIs that are not only low in cost, providing Teva with a strategic advantage and higher profitability for internally sourced products, but also capabilities in circumventing the complex patent estates of big pharma. Teva and a few other generics companies, such as Ranbaxy, and some API manufacturers, such as Hovione, are further increasing their strategic capabilities in APIs by filing their own intellectual property (IP) to cover unique processes, lower impurity profiles or other competitive advantages.

Generics companies that seek FTF opportunities in the USA or first launches in Europe (the latter do not have a period of exclusivity) must find sources of non-infringing APIs that are ready sufficiently early. 'Sufficiently early' means, on average, five to eight years ahead of the expiry or invalidation of the major constraining patent in a given market. The API manufacturer must be ready early enough to enable formulation and dossier approval in order for the generics company to be ready to launch

on the day the patent is successfully challenged or expires, often in multiple markets. A close partnership and risk sharing between the generics and API developers, in addition to strong legal work and, perhaps, luck in the courts, is essential to successfully execute an FTF or first launch strategy.

Increasingly, strategic generics players are licensing products in dose or API form from sophisticated Indian companies such as Cipla or Dr. Reddy's Laboratories (DRL), or from specialty development houses such as Synthon or Kali Labs, recently acquired by Par. Strategic companies, such as Merck Generics, utilise a combination of sophisticated, multi-country development capabilities and in-licensing to develop and launch products as successful patent challenges or on patent expiry in multiple European markets, Canada, Australia and the USA. Sometimes, generics companies not only launch on patent expiry or invalidation in multiple markets but also license out products to markets in which they are not active.

LICENSING TO GAIN NEW PRODUCTS

Cipla, one of the powerhouses of early development of blockbuster, specialised and difficult-to-synthesise drugs, is sought after as a source of new products by many major generics players, including, in the USA, Watson, IVAX, Eon (partially owned by Hexal) and others. Cipla, and a small number of other independent, highly skilled companies, are capable of complex development, support for circumventing and challenging patents in multiple markets, development of processes and IP, and ability to meet US Food and Drug Administration (FDA) and European regulatory standards, as well as low costs. Cipla, Dr. Reddy's API and Teva API, and a select few other companies, are distinguished by the ability to develop a large number of APIs simultaneously. This type of company, plus

some of the integrated regional players like Actavis in Europe and several Indian firms, have become partners of choice for business development deals involving generics companies.

So, while in-licensing of lower cost commodity blockbuster oral solids was viewed a few years ago as a way to have a full line without tying up development and manufacturing resources in a low-profit product, in-licensing has developed in the last two years as a key strategy for generics companies to achieve several goals essential to profitable growth:

- Acquire access to products for patent challenges, requiring significant investment in very early development, sophisticated IP and innovative processes to circumvent patents;
- Acquire rights to higher margin products for which there is expected to be more limited competition due to one or more barriers to entry;
- Broaden a company's internal development pipeline, especially for products requiring different drug delivery or formulation technology; and
- Acquire rights to branded generics or true branded products for selected markets.

SUPPORTING THE PIPELINE

Generics growth and consolidation have created large, publicly traded, global and regional corporations that must launch significant numbers of profitable products. Given the limited number of blockbuster drugs for which any one company can obtain exclusivity, and the consolidation in the distribution side of the business in the USA and already limited distribution in other markets such as Germany, global and regional generics companies must have huge numbers of launches and products in the development pipeline to satisfy their customers and meet investor expectations.

Table I: Lehman Brothers equity research: Generic pipelines overview (as of August 2004)

	ANDAs pending	Value \$bn	Number FTF	Value \$bn
Teva	111	72	22	19
IVAX	46	32	8	11
Sandoz	50	35		
Mylan	44	31	10	9
Taro	30	<1		
DRL	37			
Andrx	~30			
Barr	30	10		
Eon	27	13		
Par	38		8	3
Watson	29	20		
Impax	13	5	2	
APP	16			
Alpharma	15		1	2

Source: Company reports, Lehman estimates

Notes: ANDA = abbreviated new drug application; FTF = first to file; DRL = Dr. Reddy's Laboratories

Teva, the largest generics company and the company with the largest pipeline, had, according to estimates by Lehman Brothers, 112 products in the pipeline for FDA approval in the USA as of March 2004. Not included in the total is the much larger number of products in development at Teva, but not yet filed for approval.

IVAX, the second-ranking company in terms of the number of products in the pipeline for US launch, is estimated by Lehman to have 43 products in its FDA pipeline as of March 2004, followed by Sandoz at 30+ (Sandoz, a wholly owned subsidiary of Novartis, is not covered by Lehman as a separate generics company) and Mylan with an estimated 38 products in its FDA pipeline for US launch. Table 1 compares FDA pipelines of major generics companies for the USA.

The portfolio selection process for feeding the pipeline at leading generics companies focuses on several strategies to obtain profitable products. These strategies are often used in combination:

- FTF/patent challenge with a period of exclusivity

- Products with limited competition due to barriers to entry
- API backward integration
- Niche products with limited competition, usually small
- Branded niche or generic products
- Formulation/drug delivery
- Lower costs, high volume, logistics, longevity.

API ACCESS KEY TO PROFITABLE STRATEGIES

Notably, APIs are crucial to the successful execution of each strategy. Therefore, one critical attribute of a successful business development and licensing capability is the ability to obtain advantageous access to sources of APIs.

For an FTF/patent challenge, very early access to non-infringing APIs, covered by a flawless technical package, is essential. For both the generics and API companies, there is a high risk of failure because only one company can be first, although in the USA shared exclusivities are more profitable than later launches. Newport, now a Thomson business, tracks API development and commercialisation worldwide. Newport picks up API development several years prior to submission of a US or European drug master file (DMF) or a certificate of suitability (COS). For example, Newport first noted DRL's involvement with an alternative molecular form of olanzapine (Lilly's Zyprexa) in 1999, although a US DMF was not filed until 2001. Cipla was noted by Newport with a polymorph in 2000. Cipla is generally now known to be supporting IVAX, which was first to file an abbreviated new drug application (ANDA) in the USA with a Paragraph IV certification. DRL has filed a patent challenge of its own. Teva has also filed an ANDA for olanzapine and has agreed to be bound by the outcome of the DRL/IVAX court case. Teva has not announced that it developed the olanzapine API internally

and, therefore, Newport is not certain where they are sourcing the API.

For products with narrow competition and a greater likelihood of being profitable, there is usually a limitation with API supply. Often, an API is available from only a small number of sources: only one technically competent to supply regulated markets or one or two able to circumvent patents by both innovators and other generic API suppliers. Therefore, at generics companies, a premium is placed on knowledge of API sources and ability to get to an exclusive deal to secure the source of supply. These exclusive deals are increasingly being negotiated by business development executives and are more complex than traditional sourcing contracts handled by sourcing personnel.

Branded generics or specialty formulations for which clinical trials have been carried out may require different API specifications, as will different formulations or drug delivery opportunities.

In all of the above examples, the ability to find and secure a reliable, cost effective, technically competent, regulatory-compliant API source very early, and to secure exclusive, or at least contractually secure, access, is paramount to success. High-level API relationships and business development deal-making creativity are required.

CLASSIFYING GENERICS COMPANIES

Strategic generics companies can be classified based on their competence in API mergers and acquisitions (M&A), business development and licensing (BD&L) and strategic sourcing (Table 2).

Internal API development and/or dose product licensing activity are essential elements in the high number of products in the FDA approval pipelines and high number of FTF applications by the three leaders, Teva, IVAX and Sandoz.

Several of the Indian firms trying to enter the EU and US markets are having difficulty selling their older APIs, because no generics companies want to undertake the expense and regulatory risk of second sourcing. Newer Indian firms to the US and European markets which cannot sell APIs are being driven towards dose product licensing deals, which are making lower cost generics deals available to less internationally savvy US firms. Ultimately, the dose product licensing deals between newer Indian firms and middle-tier US generics companies may bring in companies with lower margin requirements and contribute to lower pricing on selected products in the USA, a subject for later inquiry. In the EU, pricing is already highly competitive. In Germany, for example, the two leading agency companies,

Table 2: Strategic generics companies: API M&A, licensing and sourcing activities

	M&A/API	Licensing	Sourcing	Purchasing	Notes
Teva	✓	✓	✓	✓	Internal API, M&A, JK Pharma India, DRL, alliances
IVAX	✓	✓	✓	✓	IVAX Americas and Czech Republic, Cipla, etc
Par	✓	✓	✓	✓	Finetech, Rhodes, Glatt, Kali, etc
Sandoz	✓	✓	✓	✓	Lek, Biochemie, other alliances
Ranbaxy	✓	✓	✓	✓	Using own APIs for strategic products for USA
DRL	✓	✓	✓	✓	APIs used highly strategically, extremely early
Apotex	✓	✓	✓	✓	Established API in Brantford
Hexal/Eon	✓	✓	✓	✓	Recently acquired Degussa plant
Mylan	✓	✓	✓	✓	Long history of early, exclusive sourcing
Watson		✓	✓	✓	Intense deal-making driving generics side
Stada		✓	✓	✓	Creative alliances, no APIs, small in USA
Alpharma		✓	✓	✓	Alpharma API higher growth, greater profits but not yet strategic for filings
Barr		✓	✓	✓	
Mallinckrodt	✓		✓	✓	

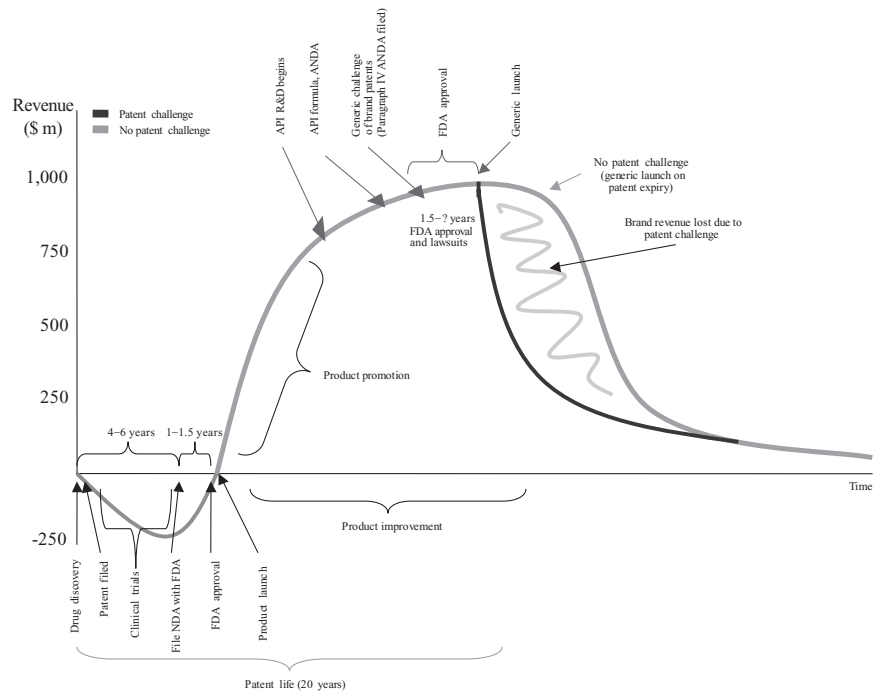


Figure 1: Life cycle of a branded pharmaceutical

Notes: ANDA = abbreviated new drug application; API = active pharmaceutical ingredient; FDA = Food and Drug Administration; NDA = new drug application; R&D = research and development

as well as leading generics companies, are experienced in negotiating dossier purchasing and licensing deals, and API sources can be switched much more easily than in the USA.

DEALS DONE EARLIER

Licensing deals are being done earlier and earlier in a product's life cycle, increasing risk. With product targeting by strategic firms into the 2013 range and beyond, licensing deals for products post-2010 are increasingly common. Evaluation of targets may start even before a branded product is launched in major markets. Figure 1 illustrates a generalised time-line for the life cycle of a branded drug product, illustrating that API development comes first and often starts as much as eight to ten years prior to brand patent expiry. The risk of supplier failure is therefore high for generics companies, and the risk of a customer

failing to gain regulatory approval or significant market share is high for API manufacturers. Expert knowledge of the API and generics players on each side, in-depth due diligence and ability to carry out risk-sharing deals to gain exclusive access are all important to profitable portfolio selection.

FEWER API CHOICES

While generics growth and profitable portfolio selection are increasingly dependent on high calibre API sources that can develop new, non-infringing, high-quality products extremely early in their life cycles, there are fewer and fewer high calibre, independent, established API manufacturers. This is due to a number of trends in the industry:

- Consolidation among API manufacturers, especially in India;

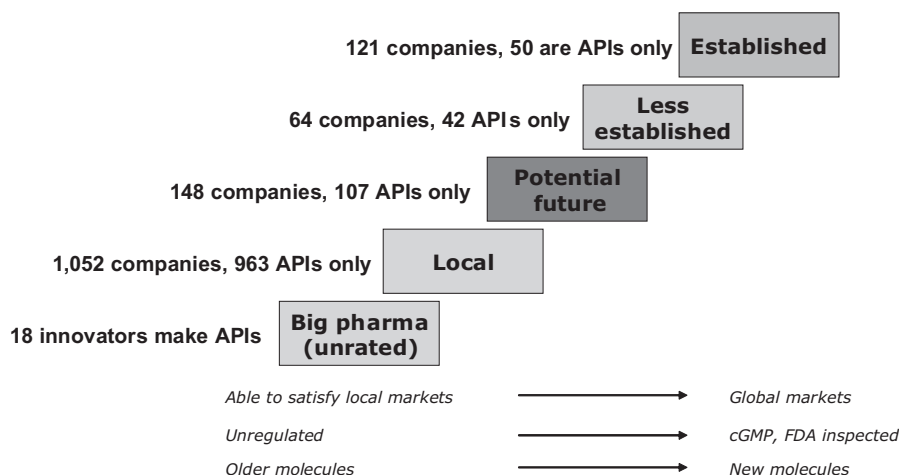


Figure 2: Number of API manufacturers which, according to Newport, are independent and capable of supplying regulated markets

Source: Newport's Horizon Global

Notes: N = 1,403; API = active pharmaceutical ingredient; cGMP = current good manufacturing practice; FDA = Food and Drug Administration

- Forward integration as companies move up the value chain and focus on selling dose products rather than APIs (eg Ranbaxy);
- Backward integration due to generics M&A, eg
 - IVAX/Chemsource
 - Novartis/Lek
 - Actavis/Fako;
- API manufacturer alliances that tie up other API manufacturers in order to handle capacity requirements, reduce costs and increase speed, such as the supply chains of Ranbaxy and DRL;
- Supplementary protection certificates that largely block European API development, leaving fewer and fewer independent European companies that compete.

In fact, as Figure 2 shows, of 1,403 API manufacturers rated by Newport in March 2004, only 92 are both independent and rated as capable of supplying regulated markets. This number includes some Indian and Chinese companies that are probably affiliated with local dose companies.

The API Manufacturer Ratings differentiate experience and capabilities of manufacturers to supply regulated markets.¹ There is movement up the value chain by lower-rated firms, while other firms are taken out of independent supply due to API or generics M&A, forward integration and supply chain alliances.

Generics companies that are managing profitable portfolios, and which can challenge or circumvent patents, need either sophisticated internal API development capabilities or business development deals with a company such as DRL, Cipla or a specialised European source.

For APIs to support products where patents are an issue, which is increasingly required in the US and EU markets, generics companies without sophisticated, internal API manufacturing capabilities can rely on a few European companies that can compete or look to India. Indian companies, such as DRL, Ranbaxy and Cipla, are notable for the number of products they develop very early in the product's life cycle with non-infringing processes.

CHINA

To date, there has been no significant development to support patent challenges in China. The many Chinese API manufacturers mostly concentrate on supplying lower cost intermediates for older molecules. There are as yet no global Chinese dose companies; however, a few Chinese dose companies are starting to look for factories outside of China to purchase. It is interesting to speculate on how long it might be before a Chinese generics dose company competes in Europe, and which market one might enter first.

STRATEGIC LICENSING DEALS

Other strategic generics licensing deals focus on smaller products or companies. Major generics companies are increasingly doing licensing deals for smaller but still profitable products with barriers to entry, limited competition or difficult formulations. Small to mid-size US generics companies are doing deals with mid-size, integrated Indian companies, such as KV, Perrigo and Lannett with Glenmark. The business development deals of today, rather than being based on lower cost of goods, are based on the lower cost of scientists and creative, non-infringing, early product development. US and EU generics companies are gaining access to new products, new formulations, IP and early development of non-infringing processes through alliances with Indian companies that effectively provide access to low-cost, high-calibre Indian scientists for research and development.

Thus generics profits and growth are increasingly dependent on effective business development. Effective business development in today's competitive, rapidly changing global marketplace means:

- Success in licensing profitable dose-form products, especially those with barriers to entry; and

- Success in obtaining exclusive access to early, high-quality, regulatory-compliant, non-infringing sources of APIs for core products, either through licensing or acquisition.

GLOBAL PLAYERS

A few generics companies in Europe, Israel and India are emerging as global and regional players, while a few US companies are vying with the European and Indian companies in the USA and, to a more limited extent, in the European market. The rapid growth of global and regional generics companies is increasing the demand for high calibre API manufacturers. There are fewer and fewer independent sources of APIs of sufficient quality, IP capabilities and creativity. Therefore, pressure to perform earlier licensing and profit-sharing deals rather than straight API purchasing contracts, as well as to acquire API capabilities, is increasing.

API M&As

The pace of API-related acquisitions is expected to increase as the growing global and regional generics companies seek to control their own specialised API development capabilities in order to leverage their ability to compete with profitable products. Examples where API capabilities have provided significant synergies in recent generics acquisitions include Teva/Sicor, Actavis/Fako, Zentiva/Slovakopharma, Novartis/Lek and Pliva/Sidmak, according to ABN AMRO.²

CONCLUSION

The traditional generics business model, where the generics company targeted blockbuster products in a single market once their patents expired, sourced APIs at arm's length, then performed formulation and dossier development and then distributed the products, has changed. Generics companies are developing increasingly sophisticated portfolio selection models,

expanding into multiple markets and using business development and licensing to obtain access to more specialised products and APIs, both through licensing and acquisition of API manufacturers.

In order to succeed in the global marketplace and meet investor expectations, generics companies must manage their portfolio selection process to focus on core products in which they have a strategic advantage that will lead to profitability. Business development is likely to play a key role either in licensing in dose-form products or in gaining access, through licensing or acquisition, to critical APIs. Generics companies must either own or acquire (and effectively run) a top-flight API manufacturer or they need a high

calibre business development and licensing capability to maintain access to APIs for core products. With increasing backward integration into API manufacturing or tight licensing/supply relationships, the generics business model is developing some aspects of the business model for big pharma.

Notes

1. The Newport API Manufacturer Rating System was developed by, and is copyright 2002–2004 to Newport Strategies, a Thomson Business. The Manufacturer Ratings are based on the API manufacturers' experience and capability in supplying major regulated markets.
2. M&A transactions courtesy of Tommy Erdei, Director, Corporate Finance-Healthcare, ABN AMRO, London, UK.