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US GENERICS MARKET- EVOLUTION OF INDIAN PLAYERS

FEBRUARY 2019

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INTRODUCTION

Generic drugs play an important role in the United States (US) system of health care, accounting for greater than 90% of total prescriptions[1] dispensed in the US. The US generics market has witnessed a transformation since 1984, post implementation of the Hatch Waxman Act.

The Hatch-Waxman Act includes a number of provisions to facilitate approval of generic drugs sold in the US by the Food and Drug Administration (FDA) and encourage generic drug entry, as described below:

1. **Abbreviated New Drug Applications (ANDAs)-** By filing ANDAs, one seeks authorization to generate generic copies of previously approved drugs (also referred to as reference drugs). Although an ANDA must contain nearly the same information as an NDA, one major advantage over an NDA is that approval does not require preclinical and clinical safety and efficacy testing. ANDA approval is given based on therapeutic equivalence of the generic drug with the reference drug, primarily similar labeling, the same active ingredient(s), bioequivalence, and the same route of administration, dosage form, and strength.

2. **180-day generic exclusivity-** This clause of the Hatch-Waxman Act is intended towards stimulating the generic drug market by providing an incentive to the first generic applicant who challenges a branded manufacturer's listed patents. In particular, the first ANDA-applicant to make a paragraph IV certification is rewarded with a 180-day period of exclusivity over other generic versions of the reference product if a court holds the patent invalid or not infringed.

The use of generics has increased substantially in the years following passage of the Hatch-Waxman Act for a number of reasons namely; a) strengthened mechanisms promoting generic use, such as tiered formularies with lower patient co-payments for generic than for brand-name drugs, and commercial insurance and public coverage plan restrictions limiting formulary coverage to generics in certain therapeutic categories; and b) state laws allowing generic forms to be substituted automatically by pharmacists for brand-name drugs prescribed by physicians, so long as physicians have not specified that the prescription must be "dispensed as written."[2]

Attractiveness of the US generics market has resulted in a rise in the number of ANDA applications received by the FDA, which has further undertaken initiatives to ease out the overall approval process. The FDA introduced Generic Drug User Fee Amendments (GDUFA) to quicken delivery of safe and effective generic drugs to the public, and reduce costs to the industry. GDUFA was instrumental in improving ANDA approval rates, that have catapulted to ~65 ANDA approvals/month from ~40 in 2012.[3]

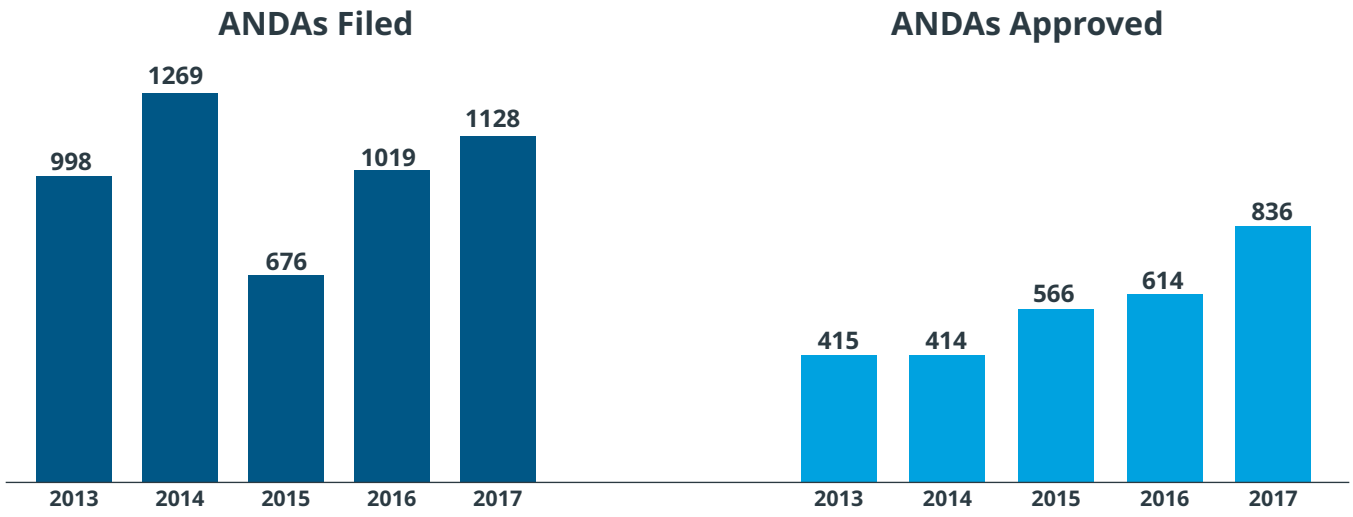
The purpose of this paper is to understand the changing pace of ANDA applications and how companies worldwide, especially Indian players, are tapping into this opportunity to successfully capture a larger chunk of the market.

ANDA FILING AND APPROVAL TREND

ANDA applications have grown marginally since 2012 and have been range bound (1,000-1,100 applications/ year)[4] (Figure 1). During this period, the highest number of ANDA applications were received in 2014. However, that was majorly due to change in FDA requirement of single exhibit batch stability data compared to three exhibit batch stability data for ANDAs filed after July 2014.

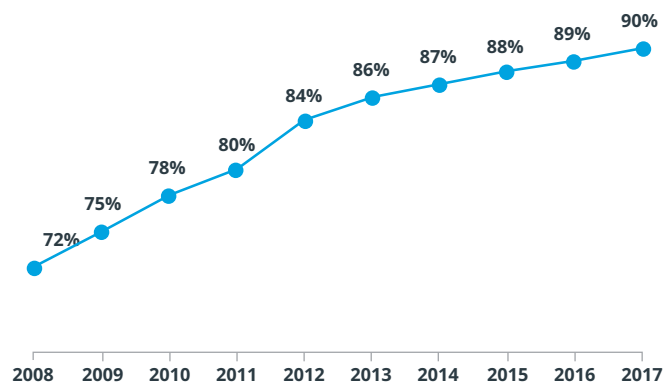
Further, with the implementation of GDUFA, FDA committed to review and act on the backlog of ANDA applications. GDUFA implementation has helped increase ANDA approval rates, that have catapulted to ~65 ANDA approvals/month from ~40 in 2012. With respect to ANDA review times, the average time for FDA to complete the first review cycle decreased from 26 months for ANDAs submitted in fiscal year 2013 to about 14 months[5]. With the incoming GDUFA II, the review time for ANDA standard application is expected to cut down further to 8-10 months.

Figure 1: Year Wise (Jan-Dec) ANDA Applications



Source: FDA ANDA Approval Data

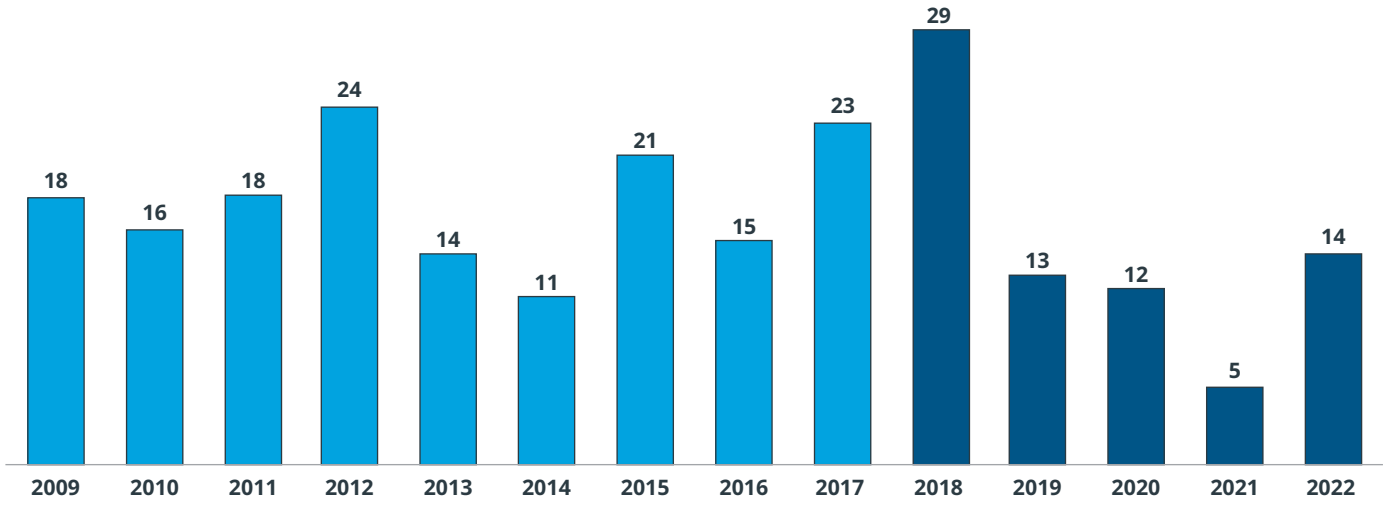
Figure 2: Generic Market Share (% of Total Rx)



Source: IQVIA Institute

The increasing ANDA approvals have resulted in increase in market share of generic drugs among prescriptions from 72% in 2008 to 90% in 2017[6] (Figure 2). This has primarily been driven by the entry of generic players across therapies and loss of exclusivity of patented products in the past decade. Within the past 5 years, drugs worth USD 83Bn have gone off-patent with another USD 72Bn worth of small molecule drugs slated to go off-patent in the next 5 years[7] (Figure 3).

Figure 3: US Small Molecule Patent Expiry Exposure (USD Bn)

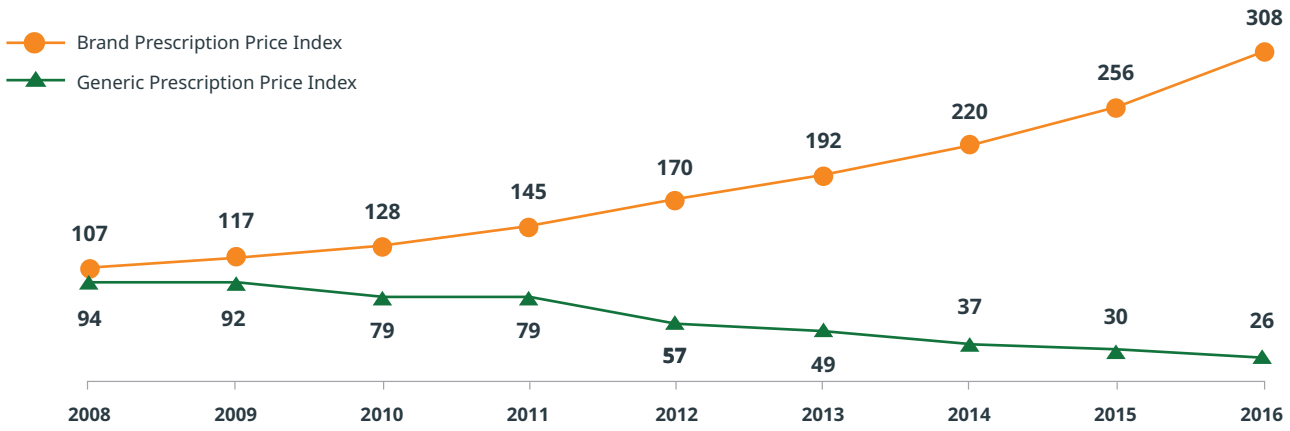


Source: IQVIA Institute

The increasing number of players filing ANDA applications for similar therapies has resulted in a highly competitive market with significant price erosion. The price impact of having more number of generic drugs for the same indication is dramatic. IQVIA analysis shows, on average, the first generic competitor prices its product at ~70%-80% of the brand-name manufacturer. However, the entry of a second generic manufacturer reduces the average generic price to ~40%-50% of the branded drug price. In recent times, multiple generic players (5 or more) have been entering at once, thereby resulting in price dips of ~50% of the innovator within the 1st year of launch. As additional generic manufacturers market the product, the prices continue to fall with average generic prices dipping to less than 5% of the innovator in products with >10 generic players.[8] Increasing competitive environment and associated price reductions resulted in a decline in generics market size from USD 77Bn to USD 71Bn between 2016 and 17.[6]

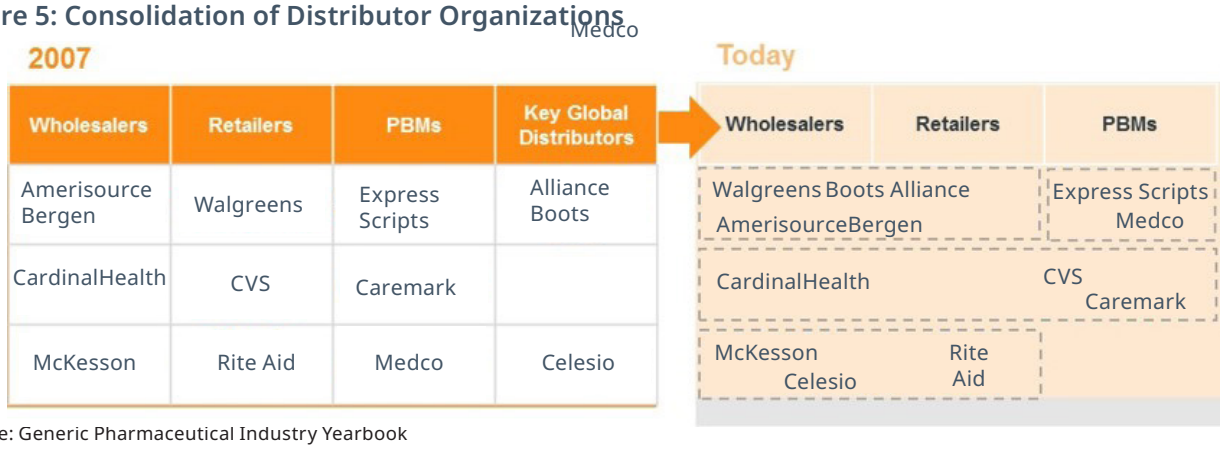
The prescription price index which measures inflation in prescription drug prices by monitoring changes in consumer prices for a fixed basket of commonly used drugs has fallen to 26.27 as opposed 93.67 in 2008 for generics[9]. Interestingly, for branded drugs it increased from 107 to 308 during the same period (Figure 4).

Figure 4: Express Scripts' Prescription Price Index



Source: Health System Tracker

Figure 5: Consolidation of Distributor Organizations



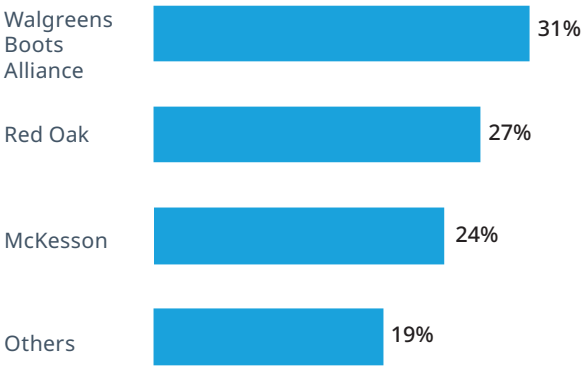
Source: Generic Pharmaceutical Industry Yearbook

The decline in generic prices has further been augmented by the rising trend in distributor consolidation. About a decade ago, US had more than 10 pharmaceutical distributors contributing to ~80% of the US generic market. However, the last decade has been witness to consolidation[10] (Figure 5) so much that the top 3 players — WBAD, Red Oak and McKesson OneStop, have contributed to >80%[11] of the US generics market (Figure 6).

With increasing consolidation in the pharma supply chain, among wholesalers, PBMs, and retail pharmacies, the bargaining power of these vertically integrated players has improved drastically, leading to pricing pressure on small and medium sized generic players. Increased bargaining power has resulted in a 4% – 5% discount in average generic sourcing cost.[8]

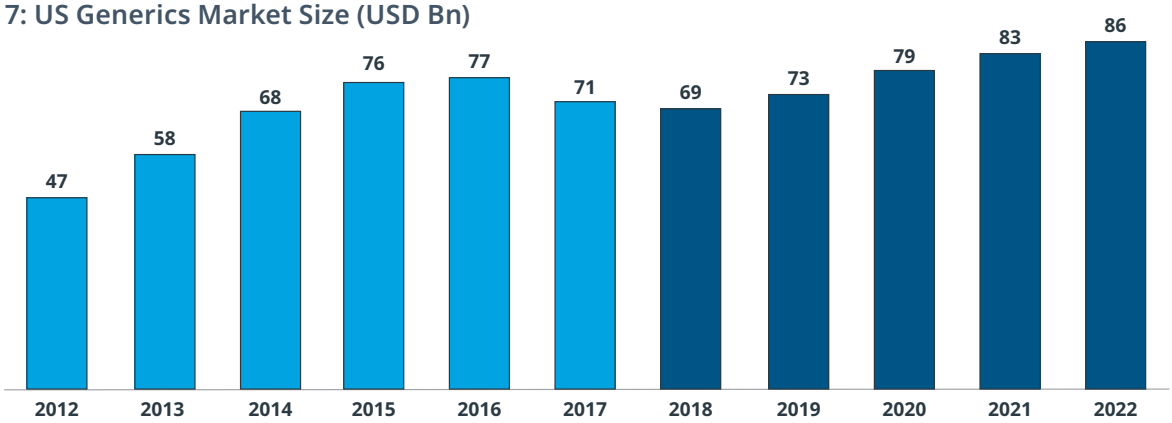
Declining prices in the generics market due to rising competition from the surge in ANDA approvals and consolidation of distributors, has taken a toll on the generics market value. Although generics market size has grown in the past from USD 47Bn in 2012 to USD 71Bn in 2017, the annual growth rate has been constantly declining from 22.8% in 2013 to 0.8% in 2016.[12] The trend is likely to continue for the next few years with even negative growth rates before the market stabilizes and comes back on track by around 2020 (Figure 7).

Figure 6: Market Share for Generics Buying Groups in 2016



Source: Longer Term Investments, UBS (2017)

Figure 7: US Generics Market Size (USD Bn)



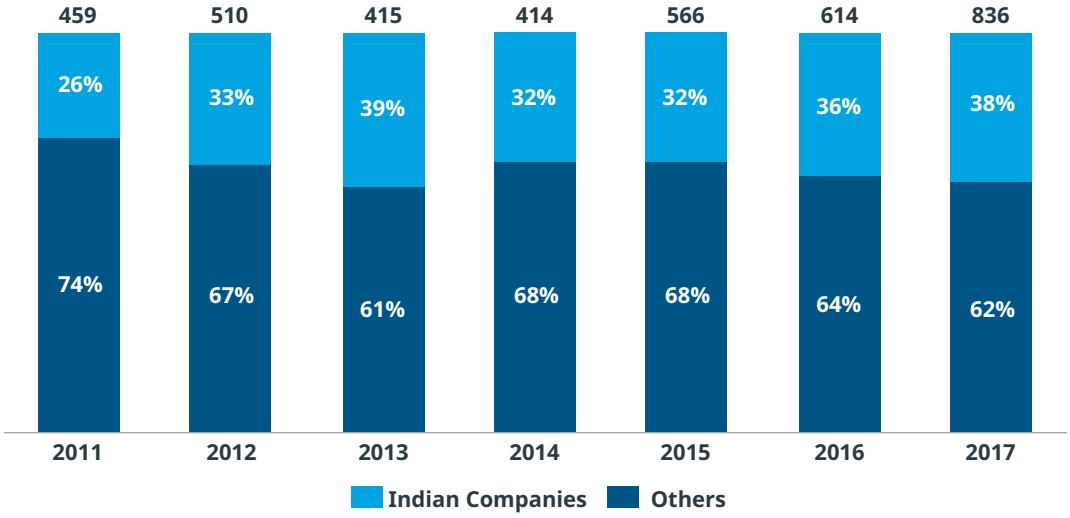
Source: IQVIA Market Prognosis

EVOLUTION OF INDIAN PLAYERS

Indian firms are rapidly expanding their presence in the list of new generic approvals by the US Food and Drug Administration (FDA). Indian pharma companies received more than 300 approvals in 2017 to launch generic drugs in the US, which is an all-time high. Out of the total ANDA approvals in the year 2016-17, Indian players have the highest share of ~40%[13] (Figure 8).

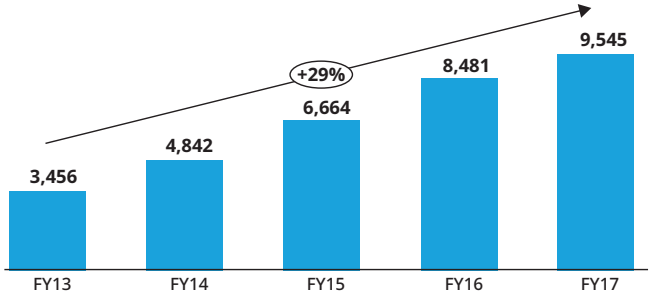
The clearances came despite regulatory pressure from the US Food and Drug Administration (FDA), and unprecedented warning letters issued to the pharma companies' facilities. All drug majors — including Zydus, Sun Pharma, Dr Reddy's and Cipla have faced regulatory warning over the last 2-3 years.[14]

Figure 8: Share of ANDA Approvals for Indian Companies



Source: FDA ANDA Approval Data

Figure 9: Aggregated Spend on R&D by Key Indian Players* (INR Cr)



*Companies considered: Lupin, Zydus, DRL, Sun, Aurobindo, Jubilant, Glenmark, Cipla and Torrent
Source: Company Annual Reports

At a company level, Zydus leads with 66 approvals in 2017, followed by Aurobindo (52), Glenmark (18), Lupin (17), Gland Pharma (16) and Cipla (10). Zydus cornered majority of US filings as its Moraiya facility came out of the USFDA scanner in June last year. Sun Pharma remained static at 10 approvals as its Halol plant was under the regulatory lens until recently.[14]

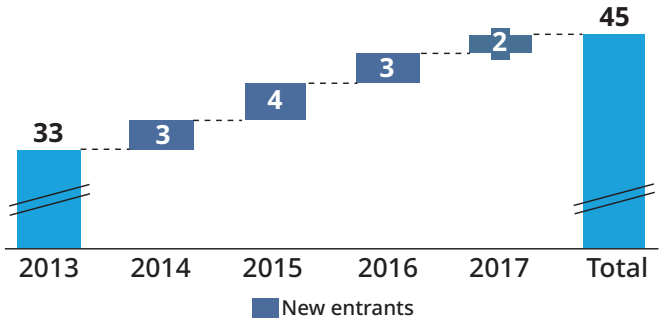
We believe that the share of Indian players will further increase to ~43%-45% over the next few years. The reason for this increase is expected to be two-fold:

1. **High R&D spend:** Large Indian players continue to invest significantly in R&D. As seen in Figure 9, leading Indian players have increased their R&D budgets by ~30% over the last few years, indicating a good launch pipeline of these players.

2. **Entry of new Indian players-** The US market continues to see entry of two to three new Indian players year after year, and these companies are expected to further drive the share of Indian players in overall ANDA approvals. Large Indian companies like Mankind and few Indian CDMOs are also planning to enter the US market.

The increasing number of product approvals and filings means that competitive intensity in the US, a major market for many Indian companies, will remain high and continue to put pressure on pricing. Indian companies are reshaping their vision to reap maximum value from the US market by extending the focus to complex formulations and launching products early.

Figure 10: New Indian Companies Receiving ANDA Approvals



Source: FDA ANDA Approval Data
*Name of new entrants in footnote

1. LAUNCH OF COMPLEX GENERICS

While the number of ANDA filings continue to remain strong for large Indian players, they have now begun transitioning the US business to specialty / complex generics where competition is relatively lower (Figure 11).

Figure 11: Complex Molecule Focus for Key Indian Players

Complex Molecule Focus	Biosimilars	Inhaled Preparations	Complex Substances	Controlled Substances	Opthalmology	Dermatology
Sun Pharma			●	●	●	●
Dr. Reddy's	●		●	●	●	●
Lupin	●	●	●	●	●	●
Aurobindo	●	●	●			●
Glenmark	●	●	●	●	●	●
Cipla		●				●

Note- Analysis based on ANDAs filed and products under development
Source: Company Annual Reports

*List of New Indian Companies Receiving ANDA Approval
2014: Rubicon, Unimark Remedies, USV
2015: Granules India, Indchemie Health, Sidmak Labs India, Windlas Healthcare
2016: Biocon, Flamingo Pharma, Shilpa Medicare
2017: MSN Labs, Pharmtak

Indian players are also taking the acquisition route to gain access to manufacturing units or proprietary therapies. Most of the large Indian players that have a significant presence in the US market have invested in acquiring companies with focus on niche therapies (complex generics) (Figure 12).

Figure 12: Key Acquisitions by Indian Players

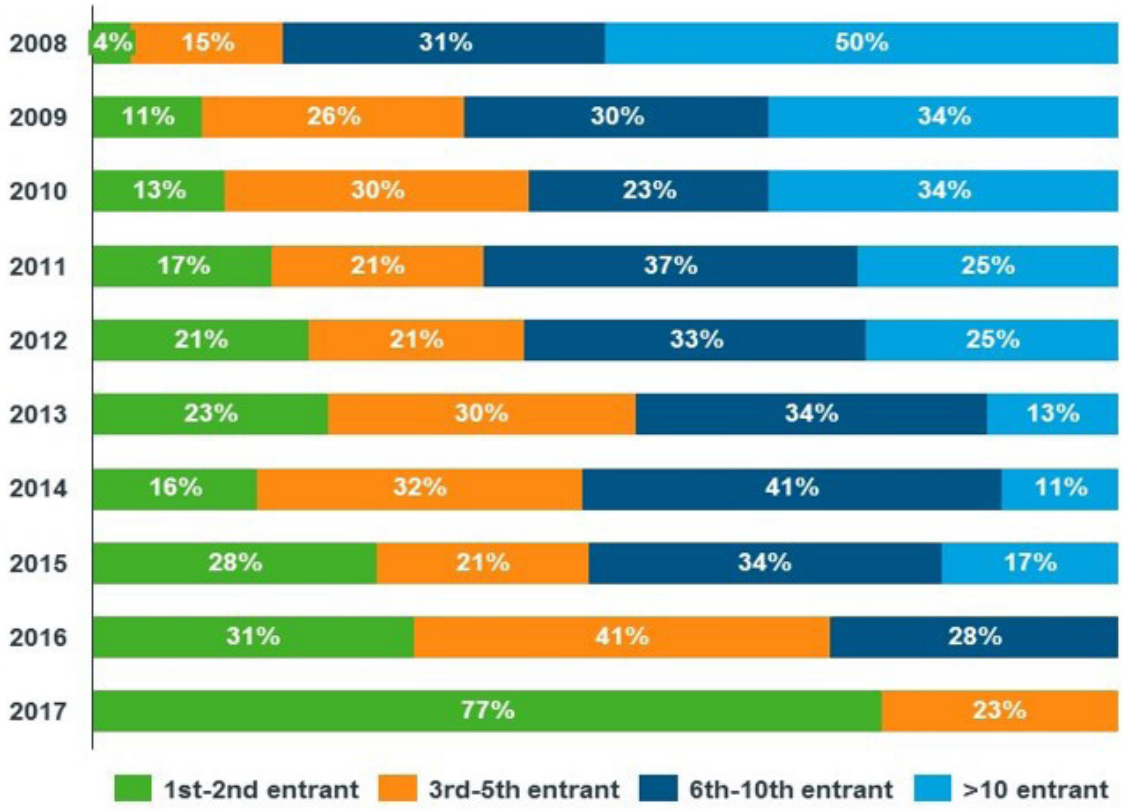
Company	Target	Access/Therapeutic Skill	Specialty/Complex/Generic
Dr. Reddy's	Habitrol (Brand acquired from Novartis)	OTC - Transdermal	Complex
Aurobindo	Acquired 4 brands from TL Pharmaceutical	Biosimilar	Complex
	Sandoz International	Dermatology and Oral Solids	Complex + Generic
Cipla	Invagen	Cardio, Anti-infectives, CNS, Anti-inflammatory and Anti-depressants	Complex
Glenmark	Uno Ciclo (Brand acquired from Institute Biochimico)	Hormonal Contraceptive	Complex
	Bouwer Bartlett	Dermatology	Complex
Lupin	Symbiomix Therapeutics	Women's Health	Complex
	Gavis Pharma	Controlled substances, Derma and Gasto	Complex
	Celon	Respiratory	Complex
	InspiRX	Respiratory	Complex
	Laboratories Grin	Ophthalmology	Complex
Sun Pharma	Ocular Technologies Sarl	Ophthalmology	Complex
	In-site Vision	Ophthalmic Specialty	Complex
	Pharmalucence	Injectables	Complex
	URL	Generic Portfolio	Generic
	Dusa	Dermatology Device	Complex

Source: Crunchbase, VCCEdge

2. ORDER OF MARKET ENTRY

Indian players have been focusing on entering the market early to gain higher share in the market. IQVIA analysis shows that until 2012, ~60% of Indian pharma players were typically among the top 6 or later companies to enter a molecule, which reduced to 50% in 2013-15. However, there has been a dramatic shift in trend in the last couple of years, with >75% of Indian players among the top 3 players to enter a generic molecule (Figure 13).

Figure 13: Order of Market Entry for Indian Players

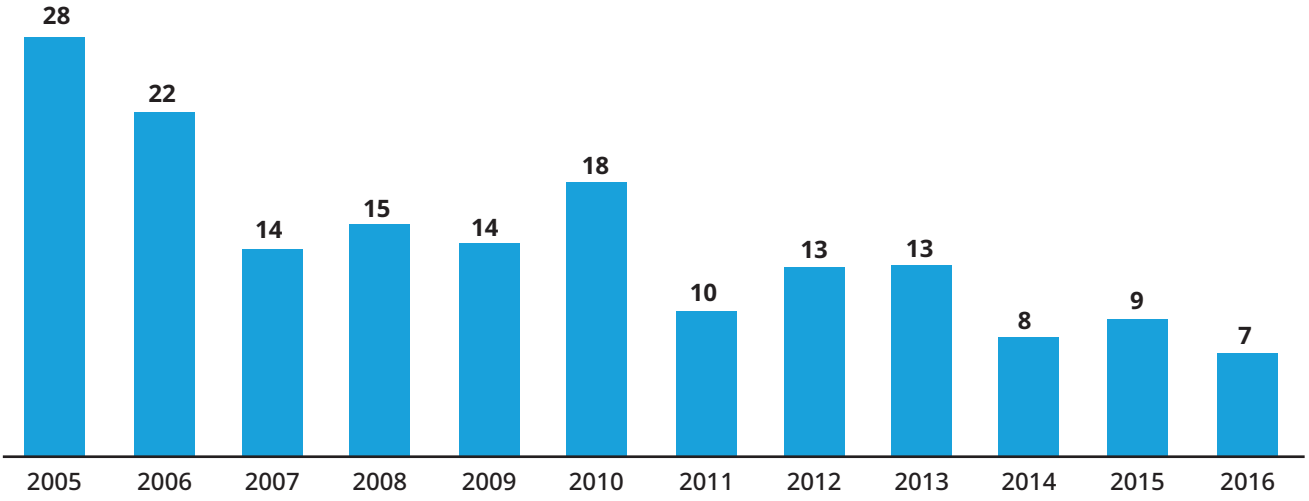


Note- Companies entering in the same month have been ranked equally

Source: IQVIA MIDAS Data

Early entry of Indian players has also been enabled by increased focus on reducing the lead time between ANDA approval and market launch. The lead time has reduced from 1.5-2 years (2006-07) to ~7-9 months (2015-16) (Figure 14).

Figure 14: Average Lead Time (in months) Between ANDA Approval and Launch for Indian Players



Source: IQVIA MIDAS Data, FDA ANDA Approval Data

KEY IMPERATIVES FOR SUCCESS OF INDIAN PLAYERS IN THE US MARKET

The rising number of players targeting the US generics market, a ramp-up in approval rates, consolidation among distributors (top 3 controlling 90% of the market) in the US and the falling number of products going off-patent over the past few years, have driven significant crowding and pricing pressure in the US generics market.

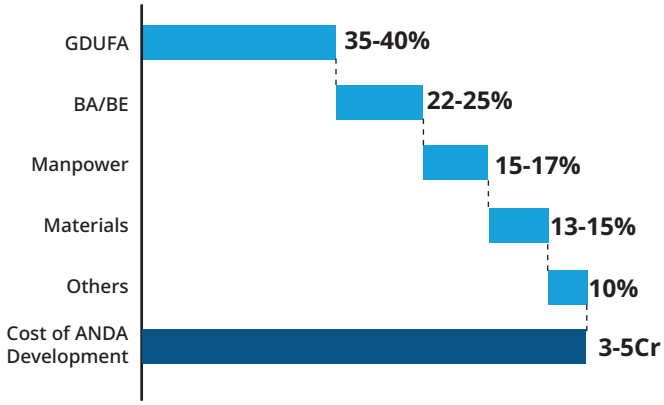
With affordable healthcare being a key focus area for the US government, the outlook for generics prices is expected to remain competitive in the near future. While all generic companies are vulnerable to pricing pressure, we believe that the smaller sized players and new entrants will be most affected due to their vanilla portfolios. Few well established pharmaceutical companies have already started pursuing strong growth trajectories, through diversification to specialty portfolio. Companies like Lupin, Sun Pharma and Aurobindo have made aggressive acquisitions in the complex molecule space and launched multiple complex generics in the recent past. Many other companies are tending towards selection of products with more complex chemistries where they foresee high market opportunity with less competition, or the possibility of differentiating themselves beyond price competitiveness. While complex generics is an emerging opportunity, Indian companies need to focus on the following to succeed in the US market:

1. RIGHT PORTFOLIO SELECTION:

When aiming for a revenue-rich portfolio, generic finished-dose companies must critically evaluate multiple criteria like loss of exclusivity, market data, availability of generics, manufacturing requirements and costs, forecasted competition etc. in order to increase the likelihood of success, and limit the risk of failure.

In the past, it has been observed that large Indian players have only launched 75-80%[13,15] of approved ANDAs. Wasted costs and time associated with product failures result in huge financial loss – typical cost of ANDA development for Indian players vary from INR 3-5 cr depending on the type of formulation (simple generic vs. complex generic) (Figure 15). This demonstrates how product identification is one of the most crucial strategic consideration for generic finished-dose companies (Figure 16).

Figure 15: Split of ANDA Development Cost



Source: Expert interactions, IQVIA Analysis

Large Indian players like Cipla are now focusing on right portfolio selection as indicated by their MD "I do not think we are going to file more than 20 products in a year, but we will choose them well. Nowadays, in the US, you think you have a very good product but there are eight companies filing the product on day one and then there are another five after that. We are running our R&D machinery really hard and the outcome may not be what we want. So we will try and do less filings but focus on the ones that are lot more complex."[16]

Figure 16: Rating of Indian Players Based on Number of ANDAs Launched to ANDAs Approved

Company	Alembic	Aurobindo	Cipla	Dr. Reddy's	Glenmark	Jubilant	Lupin	Sun Pharma	Torrent Pharma
ANDA Launch/Approved Rating									

High Medium Low

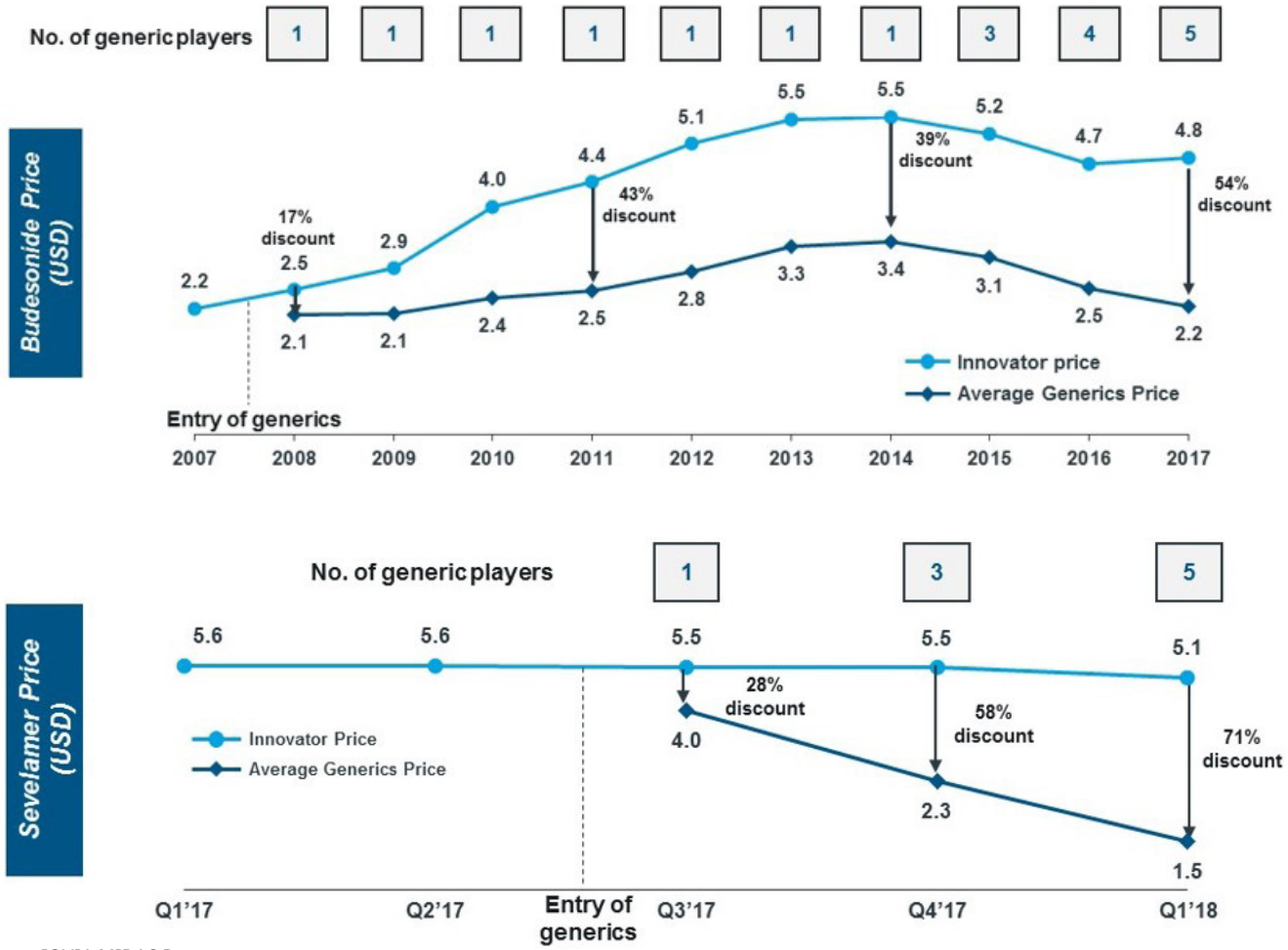
Note- Only molecules directly launched by the parent company between 2005 to 2016 considered

Source: IQVIA MIDAS Data, FDA ANDA Approval Data

2. TIME-TO-MARKET:

To limit competition and prolong high profitability business, Indian pharma companies focusing on US market are building complex generics pipeline. However, with increasing number of players focusing on this space, price erosion is expected to happen faster than before. Historically, price erosion was limited due to lower competition - Budesonide (inhalation suspension) had just 1 generic player in the market until 6 years of LoE. However, of late, multiple players are entering the complex generics market, as can be seen in the case of Sevelamer, where generic prices dropped from 72% of innovator's price to 29% within three quarters of launch due to entry of 5 generic players (Figure 17) .

Figure 17: Complex-Generics Price Comparison

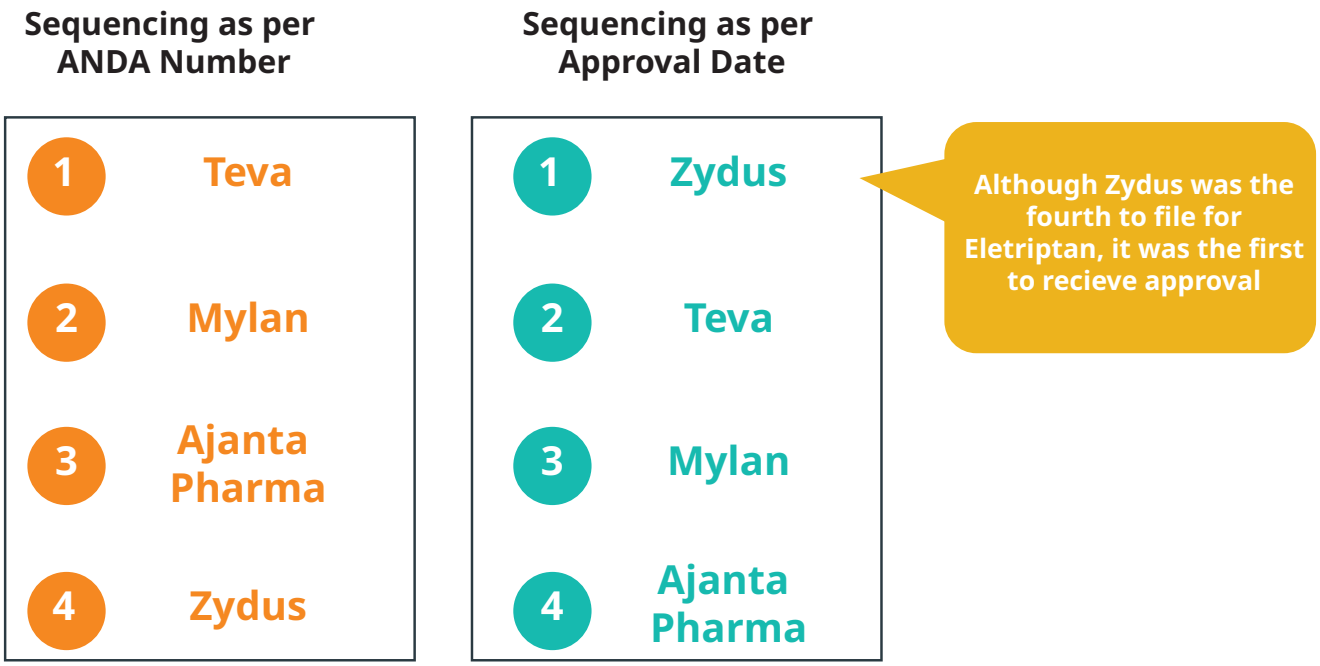


Source: IQVIA MIDAS Data

As a result, lead time to approval becomes very critical, which in turn is a function of timing of filing, quality of work done to prove bioequivalence and establishing robust manufacturing processes that would enable up-scaling from lab to commercial level.

Submission of complete and satisfactory data can substantially reduce time of correspondence between ANDA filing company and FDA, thereby reducing approval time. We highlight the case of Eletriptan (Figure 18), where Zydus was behind peers in terms of filing ANDA with USFDA (on the basis of application number). However, due to exhaustive and satisfactory data submitted by Zydus, it was the first to get its ANDA approved by USFDA (Figure 18). In the current 55% volume market share for Eletriptan generics, Zydus contributes 25%[15]. Thus, better the ANDA application, faster is the time to market and higher is the scope for enjoying benefits post approval.

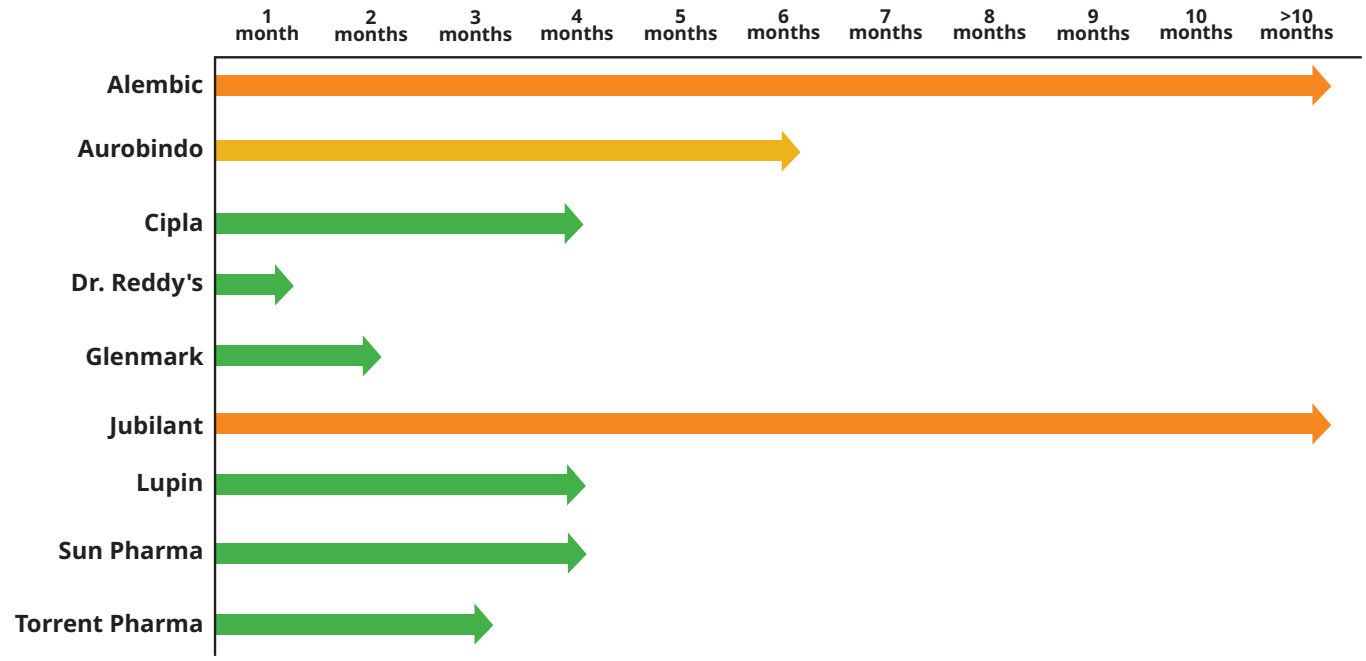
Figure 18: Approval Timeline for Eletriptan



Source: FDA ANDA Approval Data

Timely approval needs to be backed by timely launch of the product in the market, as delay in launching of generics post approval has the potential of hampering the benefits that a company can enjoy in the market. The lag between ANDA approval to actual market launch varies across Indian players from 1 month to >10 months (Figure 19). Companies like Dr. Reddy's and Glenmark have leveraged strong supply chain setups to ensure launches within 2 months of approvals.[13,15]

Figure 19: Average Time from ANDA Approval to Market Launch



Note- Timeline based on products approved and launched between 2013 to 2016. Considered products directly launched by the parent company

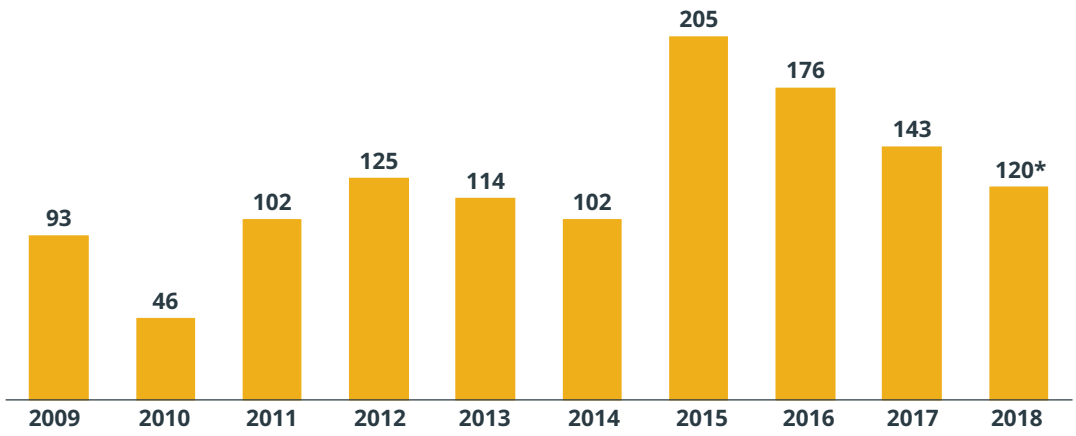
Source: FDA ANDA Approval Data, IQVIA MIDAS Data

3. REGULATORY COMPLIANCE:

Adherence to the cGMP (current good manufacturing practices) as per FDA guidelines, is sacrosanct to prevent regulatory clampdown on company facilities. India has the highest number of FDA approved finished dosage facilities (~200)[17] . Hence, the relevance of Indian facilities is high in the global context (Figure 20). US FDA has increased the frequency of its inspections to once or even twice a year, compared to once in two to three years earlier. The prior intimation time for plant inspection has also been slashed from 25-30 days to as little as 24 hours[18].

Further, the FDA has intensified scrutiny on drug manufacturing facilities as companies are now being penalized for lapses such as inappropriate clothing of employees, improper washing conditions and inadequate lighting, apart from issues relating to data integrity, batch failure investigations or improper quality control systems.

Figure 20: Number of Inspections Conducted by USFDA in India



*Data till Aug | Note- Only considered inspections and audits for drug quality assurance purposes

Source: US FDA Inspections and Audits report

Companies failing to adhere to FDA guidelines have faced the brunt of not getting timely approvals in the past. For instance, Sun Pharma's approval count for last year remained static at 10 as its Halol plant remained under the regulatory scanner of FDA.

We believe that although the US generic market will be challenging over the medium term, given the pricing and competition risks, Indian companies with clear visibility in terms of US pipeline, in advanced stage of making investments in complex molecule, robust supply chain setups in the US and strong internal quality processes in compliance with FDA guidelines, are bound to succeed.

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