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Biosimilars

How can we realize the $ 240 billion opportunity

White Paper

October, 2016

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October 2016

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ACKNOWLEDGEMENT

It gives me immense pleasure that ASSOCHAM in association with Department of Pharmaceuticals, Government of India is organizing Conference on "BioPharma: Biosimilars & Biogenerics" at Hyderabad.

Biotechnology refers to the application of scientific techniques using living organisms or their parts to make or modify plants, animals, microorganisms or environment to enhance their performance and values. In the recent years biotechnology has emerged as a major focal point for the developed as well as the developing nations. It has a greater vision to sectors such as human health, agriculture and environmental science for the future. The Indian biotech industry holds about 2 per cent share of the global biotech industry. The Indian biotech industry grew 16.28 per cent in FY14; the total industry size was $ 5 Bn at the end of the financial year and it reached $ 7 Bn in FY15.

The Indian Biotechnology sector is presently divided into five segments based on the products and services offered. These segments are Bio-Pharmaceuticals, Bio-Services, Bio- Agriculture, Bio-Industrial and Bio-Informatics. Biopharmaceuticals are medical drugs produced using biotechnology. Bio-Pharma is the largest sector contributing to 62% of the total revenue followed by Bio-Services, Bio-Agri and Bio-Industrial sectors which contribute 18%, 15% and 4% respectively while Bio-Informatics is still at a nascent stage contributing to only 1% of the total revenue.

I am sure that this Conference will deliberate on all issues relating to the growth of Biotechnology specifically Biopharmaceuticals in India. I also extend my heartiest thanks to all the stakeholders for lending their support to this Symposium. I would also like to thank our Knowledge Partner of this Symposium "SATHGURU" for its wonderful efforts in putting up this comprehensive report on all the subjects pertaining to the Indian BioPharma Industry.

I also acknowledge the efforts put in by Sandeep Kochhar and his team members Anshul Gupta and Karanveer Singh, for organizing this Conference.

I not only wish this Conference a great success but also assume that ASSOCHAM shall continue to organize such programs for larger public benefits with a great degree of excellence.

D S Rawat
Secretary General -ASSOCHAM

Biosimilars – How can we realize the $ 240 Bn Opportunity

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Executive Summary

The growing share of biologics and the sizeable biosimilars opportunity

Biologics have now gained significant traction in pharmaceutical industry with more than $150 Bn in global sales in 2013. 48% of sales come from 11 biologics that face loss of exclusivity over the next few years. This along with the increasing worldwide focus on improving access and reducing cost of care, presents an attractive biosimilars opportunity.

The biosimilars opportunity is nascent today and the 2016 estimated market size was only $2.2 bn. However, the recent USFDA approvals and market penetration stories emerging from Europe herald in the next phase of growth in biosimilars. Based on our analysis of the currently approved biologic drugs, clinical pipeline and expectations around price erosion and market penetration, we estimate that global market for biosimilars will be $ 240 Bn by 2030 in the optimistic scenario and the Indian domestic market could be north of $ 35 Bn.

Critical elements for success – technology, regulatory and market access

Technology: Technology has historically been one of the largest hurdles for entry into biosimilars. Over the last decade, several companies across the world have developed platform expertise across microbial and mammalian platforms. While technology continues to be an important cog in the wheel, access to technology is becoming less of a challenge with a vibrant development landscape and significant collaboration possibilities.

Regulatory: Regulatory landscape for biosimilars has been evolving with the global pioneer EMA setting the trend. While USFDA has been slower to warm up to biosimilars, recent approvals in 2016 are symbolic of the world's largest market now being more receptive to biosimilars. The RoW landscape is a mix of countries with varying levels of regulatory maturity and market access considerations. The Indian market has benefited from proactive release of guidelines, a forthcoming regulator and a recent revision in guidelines to make it more aligned with global regulations.

Market Access: While regulatory ambiguity is declining, there is still need for structural evolution across regions on critical market access elements such as interchangeability. As the frontrunner biosimilar market in the world, EMA continues to set the trend on market adoption as well. With level of price erosion breaching 60% in certain European countries, the myth of 20% price erosion in biosimilars is now shattered. However, despite the steep price erosion, Europe sets an optimistic benchmark for market penetration with share of biosimilar being greater than 50% of in several countries. Overall, we anticipate that next five years will provide a clear picture of market access considerations across developed markets and will pave the wave for greater industry investments.

RoW markets offer lower regulatory barriers and are relatively easier to access. Given the low penetration of biologics in RoW markets due the high prices, biosimilars offer the promise of affordable alternatives that can expand access to vital drugs in these markets. However,

this promise translating to accelerated market expansion in these countries will be critical to establish financial sustainability of RoW focused biosimilar investments. We would like to highlight that current levels of market expansion in several RoW markets is far from encouraging. Hence we believe that commercial strategies and policy efforts to expand markets will be the primary driver of RoW market success in biosimilars.

Path to success

Leveraging the current vibrant landscape in India: Several large Indian companies have invested in biosimilars and have developed in-house product development capability. They are largely focused on India and RoW markets as initial targets but intend to aim for the developed markets in the future. Indian biosimilar segment has today built a foundation on which global success can be steered with appropriate commercial strategies and policy environment required to succeed in this capital intensive and time sensitive opportunity.

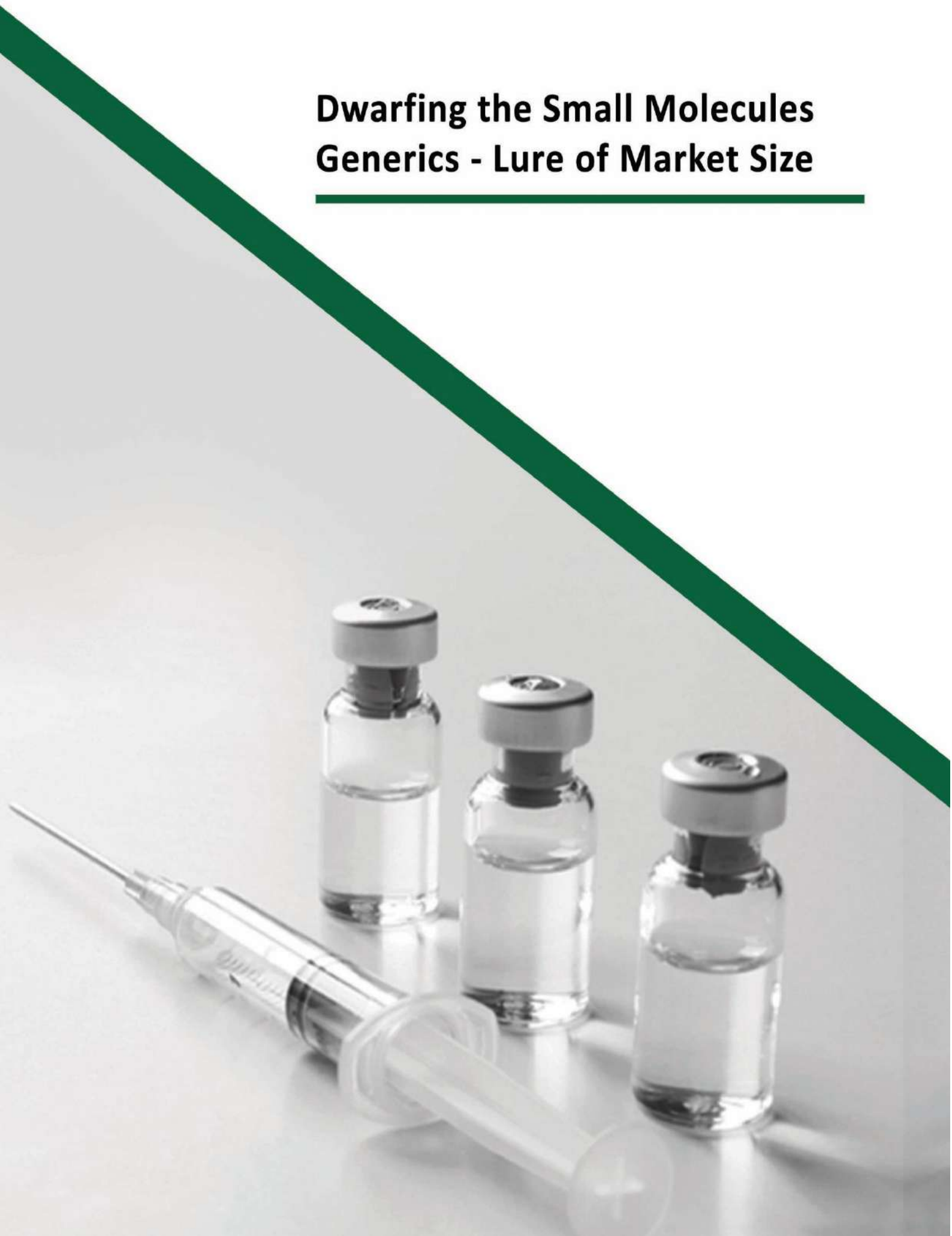
The collaboration imperative: We believe collaborations will be fundamental to Indian industry's success in biosimilars, particularly to address following three challenges:

1. **Accelerating time to market:** While Indian industry has now developed high level of technical capability, given the time sensitivity in biosimilars, asset level collaborations for technology access could accelerate time to market and global competitiveness.
2. **Breaking into developed markets through risk sharing:** US and Europe today represent bulk of the biosimilar opportunity. Given average investment of more than $ 150 Mn per asset, to build a portfolio of around 5 assets a company has to shoulder binary risk of $ 600 Mn to $ 1 Bn. Risk sharing co-investment collaborations, both with MNCs as well as with other Indian companies can help break this barrier to entry.
3. **Expanding RoW markets to build commercial sustainability:** While RoW markets are easier to access, financial sustainability will be elusive until markets expand to their true potential. Collaborations amongst Indian companies as well as with RoW companies will be critical to pool resources to expand markets and render RoW attractive on its own.

Policy measures:

At the current threshold, following impetus from the Government could enable Indian industry to achieve global success in biosimilars in the next decade. A large quantum of binary risk in the capital intensive product development pathway continues to be a deterrent for industry. Non-dilutive funding mechanisms that offer sizeable funding could help make risk palatable, create initial pipeline of regulated market launches and seed sustainable engagement in the segment. Such non-dilutive funding mechanisms should be extended to technology acquisition as well. While India benefits from timely adoption of regulatory guidelines, there is need to address concerns around time consuming processes and delays that render biosimilar companies and CMOs non-competitive in the global landscape. Lastly, globally comparable fiscal incentives will be important in light of efforts from several other countries to attract global investments in biological manufacturing infrastructure.

Dwarfing the Small Molecules Generics - Lure of Market Size



I. Dwarfing the Small Molecules Generics - Lure of Market Size

Biologics are therapeutic proteins, such as monoclonal antibodies (mAbs), that are manufactured from natural sources, including living "host" systems, such as human and animal cells, yeast, and bacteria. Engagement in biologics has been intensifying with the segment emerging as the primary growth driver in the overall pharmaceutical industry. Today, biologics represent more than 20% of the total pharmaceutical industry, valued at $987 Bn.

There has also been sizable shift in investment from the historically dominant small molecules to large molecule biologics. Consequently, there has been a consistent increase in the number of biologic drugs approved. As illustrated alongside, the average number of New Biologic Entities (NBEs) approved by USFDA surged from 3.2 in 2004-2008 to 5.8 in 2009-2013 and again almost doubled to 11.5 in 2014-2015.

The significant increase in number of biologic drugs approved in 2014 and 2015 resulted in an overall growth in number of drugs approved. While biologics are gaining a larger share of new therapeutic solutions being approved, they are reshaping landscape of pharmaceutical industry and expanding the market as a whole.

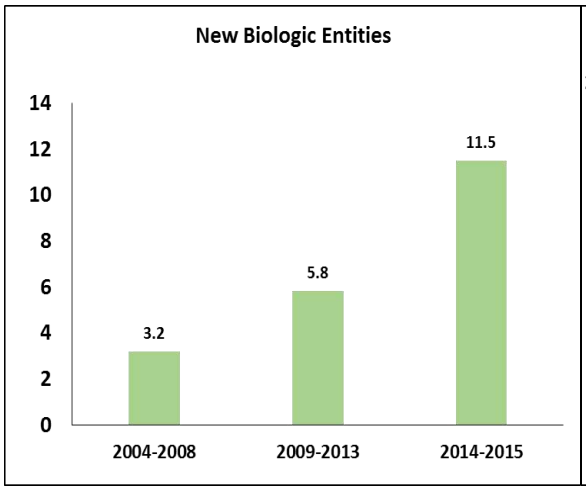


Figure 1: New Biologic Entities approved
Source: US FDA

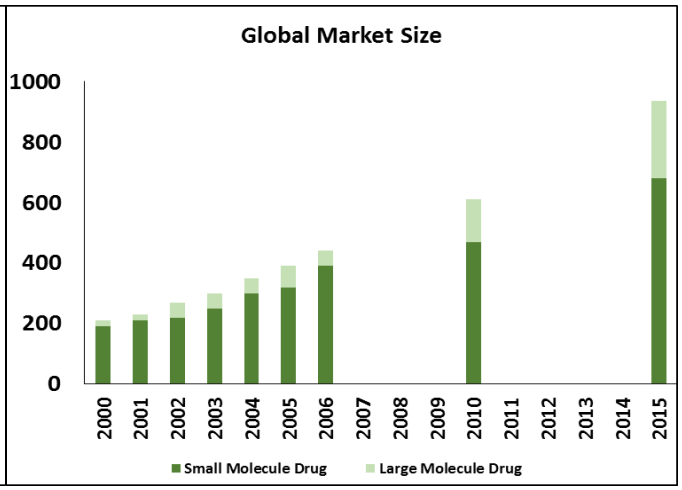


Figure 2: Worldwide Market Size of Drugs
Source: BCC Research, 2015

1. The biosimilar opportunity

About 40% of total biologic sales come from 12 biologics that face loss of exclusivity over the next 5 years, valued at almost $55 billion in sales. Top 10 biologicals alone, will open up around $23 billion in sales to competition from biosimilars.

Historically, pharmaceutical patent expiry has opened up a significant market for generic drugs. With increasing transformation in the overall pharmaceutical landscape towards

biologics, biosimilars or follow-on biologics offer a hard to ignore opportunity for innovative biotech and generic companies alike.

US FDA defines biosimilars as: *"A biosimilar is a biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."*

In 2013, thirty years after the Hatch-Waxman Act was signed into law in the US, generics account for 86% of all dispensed retail prescriptions in the US. They are widely attributed to have saved the economy close to $200 billion. The considerations around cost savings, affordability and access intensify multifold in the case of biologics. While biologics are addressing significant unmet medical needs, they are expensive, a burden to the payors and patients and unaffordable to many. Some of these therapies cost upwards of $100,000 per treatment course on an annualized basis. While biosimilars today are at a rather nascent pedestal, the potential to rationalize spending on drugs in developed economies and provide access in developing economies is expected to support the level of engagement that could dwarf the small molecule generics by 2030.

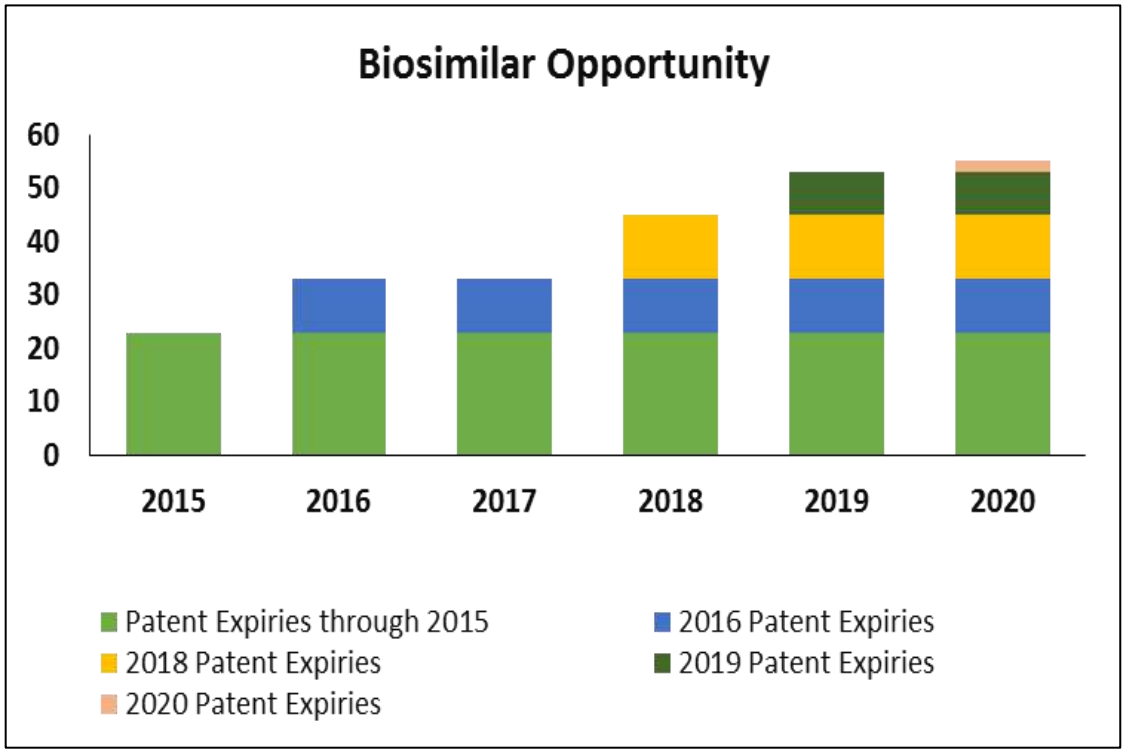


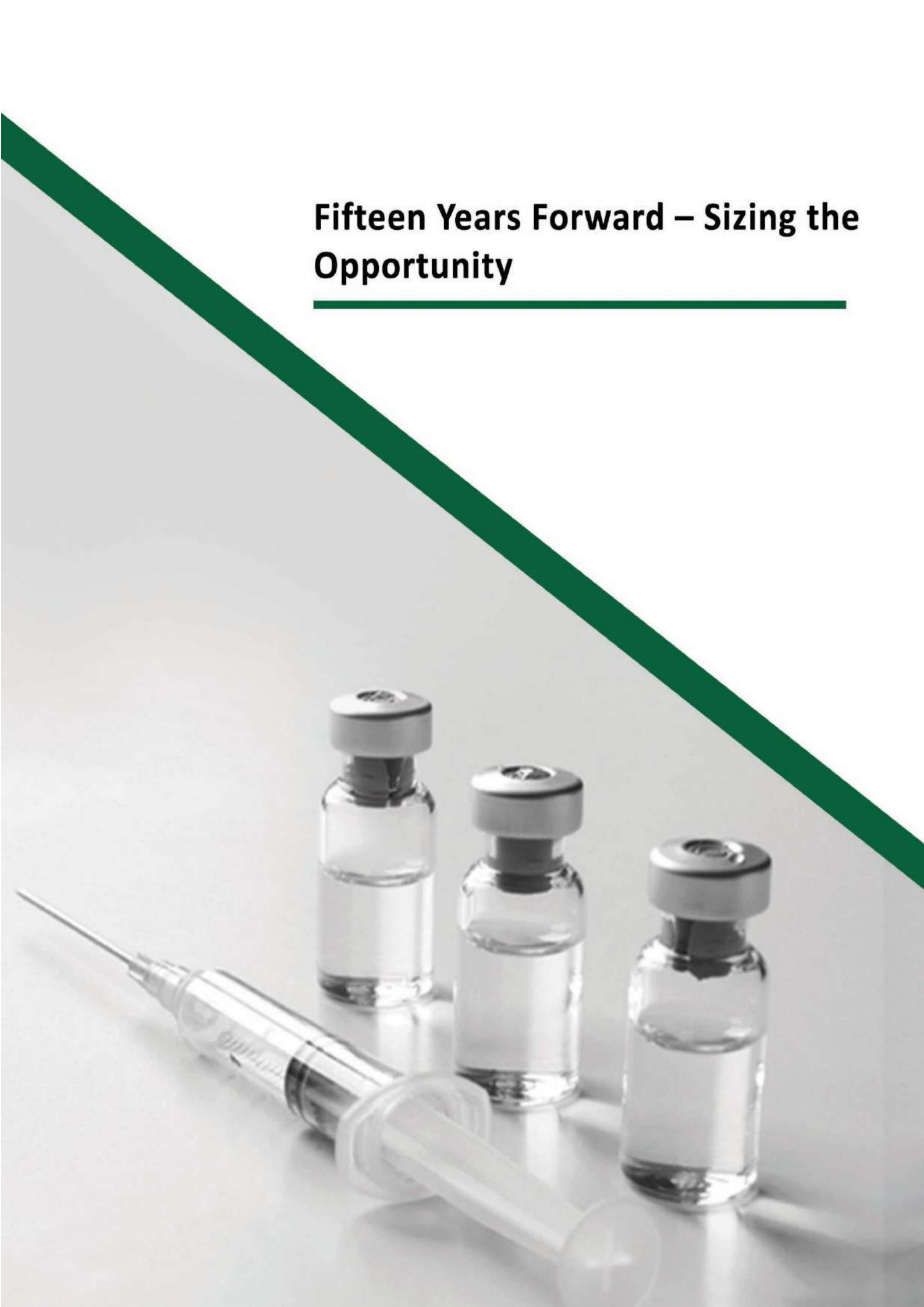
Figure 3: Biosimilar Opportunity in $ Bn
Source: Company Reports, JP Morgan

2. Near term opportunity

Just as generics emerged as a powerful force in the last two decades, for many in the pharma industry, biosimilars will be a strong agent for change in the future—either through disruption or innovation.

In general, biosimilars will be a higher-risk but also higher-rewarded business as compared to classic generic drugs. Biosimilars represent a new paradigm in the market and the pace of rollout and ultimate penetration of these products is anticipated to ramp up with increasing regulatory certainty and stakeholder acceptance. With the current set of blockbusters going off patent by 2018 there is a sizeable opportunity of ~$50 Bn which will open up for biosimilars.

Fifteen Years Forward – Sizing the Opportunity



II. Fifteen Years Forward – Sizing the Opportunity

1. Sizing the Global Market

While there has been palpable excitement around biosimilars and dense industry engagement across global regions, biosimilars still stand at a relatively nascent pedestal in most markets. Regulatory and commercial ambiguity still cloud the market and the estimated 2016 market size is only around $2.2 Bn. With the slew of landmark USFDA approvals to date in 2016 and the emergence of more penetration success stories in several EU countries, future realizable potential of a sizable biosimilar opportunity becomes more tangible.

We estimated the 2030 market size of the biosimilar opportunity based on currently approved biologic drugs and pipeline analysis for anticipated approvals during the period.

In the optimistic scenario, we anticipate that the total Biosimilars market will cross market size of ~$240 Bn by 2030 as compared to the current market size of $2.2Bn in 2016 with a CAGR of 36%.

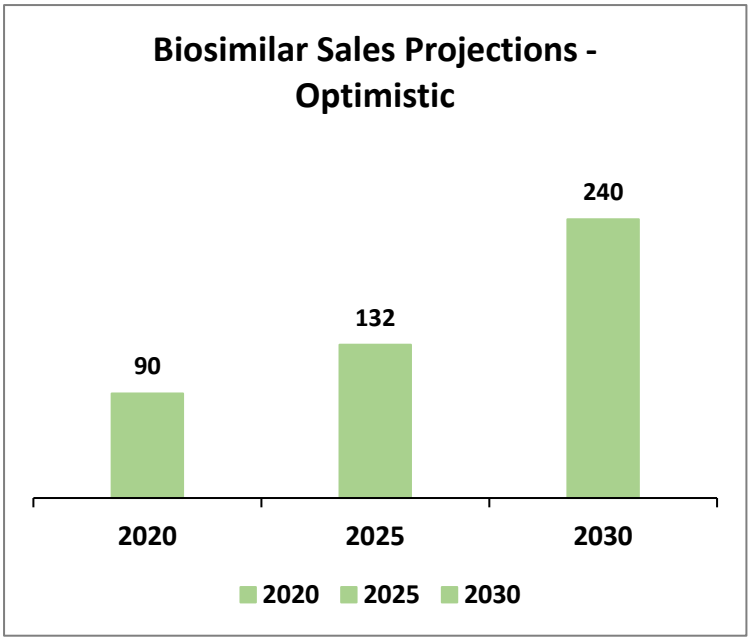


Figure 4: Biosimilar Sales Projections - Optimistic
Source: Sathguru's Internal Research

Assuming a price reduction of ~60%, Loss of market to new therapies at 20% and an 5% increase in volume due to lower prices we see that the total Biosimilars market approximately doubles itself in five years and presents a highly lucrative opportunity for all interested parties even if they have missed the 1st and 2nd wave of Biosimilar opportunity. With the recent regulatory developments and technology availability, we believe there is a high probability of markets reaching the projected potential.

Since the first approval of Somatropin biosimilars in 2006, the number of approved biosimilars have gone up substantially with currently 20 biosimilars approved in Europe along with around 10 approved in Japan and 64 approved in India. Also the current filings for biosimilars approval and the no. of products in the pipeline have gone up as shown in the figure below.

We discuss below key elements that underline our market acceptance and penetration assumptions:

a. **Regulatory Clarity:** Regulatory uncertainty and its consequent impact on non-clinical and clinical development effort, time to market, and size of potential market once approved has been one of the primary concerns deterring higher industry investments in biosimilars. However, there is gradually increasing regulatory clarity and we anticipate that the next three to five years will present a clear picture for biosimilar pathways across the world. In the recent past, more countries have come up with guidelines for approval of biosimilars, certain countries have released new versions of guidelines and most importantly, the USFDA has warmed up to biosimilars and has thereby sent positive regulatory signals in the largest biologics market of the world. We project a near term growth in biosimilar applications and approvals as well as a sustained momentum during the next two decades (please refer to Regulatory Landscape section for a detailed analysis of this change).

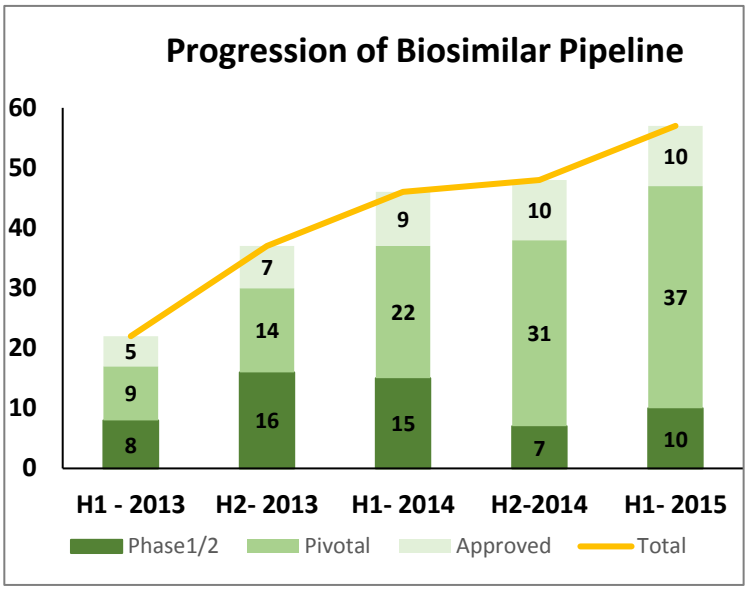


Figure 5: Progression of Clinical Biosimilar Pipeline
Source: Bernstein, Biosimilars: Who is doing what? April 2015

b. **Market Acceptance & Clinician Confidence:** While biosimilars still need to cross the abyss of market acceptance, early success in initial market penetration struggles present great scope for optimism. For e.g. in Europe, filgrastim (Neupogen) biosimilars have captured >50% share of short acting G-CSF market and >75% of the filgrastim market within 5 years of launch. We now have early acceptance and substitution rates emerging for monoclonal antibodies and again Europe leads the way with setting the bar on driving clinician confidence through a concerted effort. With the passage of

> *"Now, there are certain biosimilars in which I don't really care if it's going to be AB-rated because it's episodes of care. So you take a white cell stimulator- when you have low white cells, it's a unique episode; I can put you on any biosimilar for that episode of care."*
>
> *- Dr. Steven Miller, Express Scripts CMO at 2015 Analyst Day*

time and increasing confidence in Biosimilars we expect that these numbers will only go up in future, and the IMS data from the absorption of biosimilars suggests the same:

EU Consolidated		
Molecule	**Volume Increase (2015/the year before biosimilar launch)**	**Year of First Launch**
EPO	71%	2007
G-CSF	99%	2007
HGH	38%	2007
anti-TNF	20%	2013
Follitropin Alpha	10%	2014
Insulin Glargine	6%	2015

Source: IMS MAT Mar'15 Data

c. **Payor Thrust:** With an increasing pressure on governments and payors in reimbursement markets to bring down the healthcare costs there is an increased thrust for use of biosimilars to cut down on the costs and this will eventually drive high biosimilars uptake in these markets.

2. Indian Opportunity

India is very well placed to tap into the biosimilars opportunity that will come up in the next 15 years. Several Indian firms such as DRL, Biocon, Zydus, Intas, Aurbindo and others have already made concerted investments and are at an advantageous position to participate in this lucrative market.

We foresee Indian companies tapping the biosimilars advantage across three market segments:

a. **Catering to the domestic market:** With the introduction of a new regulatory policy in India and increased affordability that biosimilars offer we believe the domestic market will grow at an accelerated pace. As a largely out-of-pocket market, majority of population is cut off from biologic treatment possibilities due to the high price and biosimilars offer the promise of healthcare access.

We estimate that, in optimistic scenario, domestic market itself will grow to ~$40Bn by 2030.

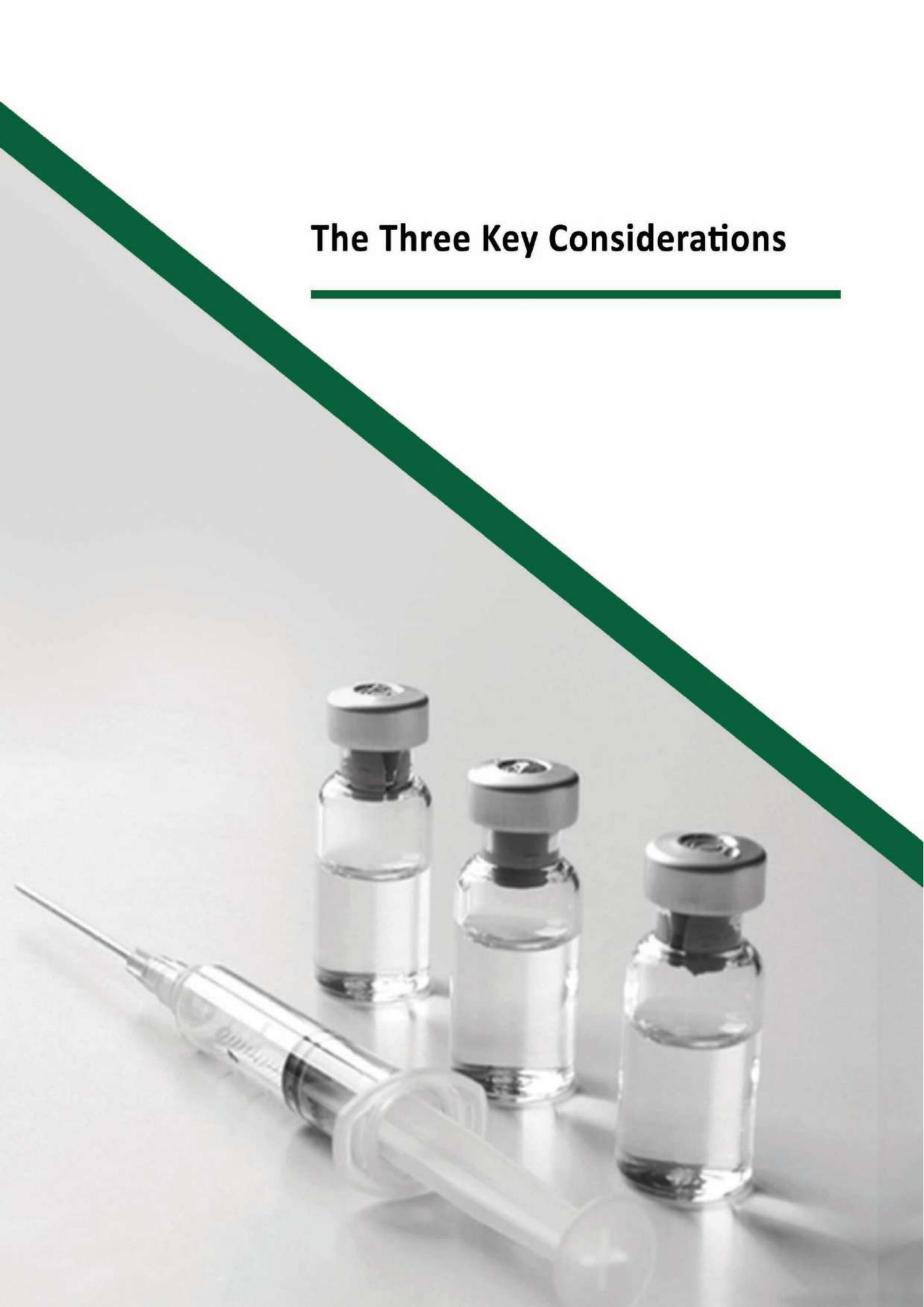
b. **As a contract manufacturing hub:** With the Indian pharma industry already earning global recognition for itself as a low cost manufacturer with quality and the current flurry of investments in biosimilars manufacturing in both eukaryotic and prokaryotic

cell-lines, we believe Indian industry has a very high potential to become the contract manufacturing hub for biosimilars if thrust is put in this direction.

c. **Catering to global markets:** With the current capacity and technological knowhow for biosimilars Indian biopharmaceutical industry is in a very good position to export these complex products to the regulated and semi-regulated markets. With lower risks and entry barriers, RoW markets present an exciting near term opportunity for this industry whereas the regulated markets with higher returns and increased risks present a medium to long term opportunity for this sector.

Currently the value of contract manufacturing and exports from India is close to $50Mn and we see a high possibility of this market achieving a revenue of ~$6 Bn by 2030, growing at a CAGR of 38%.

The Three Key Considerations



III. The Three Key Considerations

1. Technology

The Historical perspective: Historically, the complexity of manufacturing biologics and biosimilars has been one of the largest hurdles to participating in the biosimilars opportunity. Development of biosimilars is much more challenging than the development of small-molecule generics, due to the greater complexity of biological drugs (chemical structure, analytical characterization) and the complex manufacturing process. Large biopharma companies that have commercialized innovator biologics and benefit from proprietary knowledge and experience in developing and manufacturing biologics had a considerable advantage over new companies with no such manufacturing experience. Most small molecule generic companies competing in the segment have traversed the difficult journey of initiating internal engagements and/or structuring upstream technology collaborations. Technology for developing biosimilars still continues to be a critical challenge as well an opportunity for value creation.

Current technology development landscape: There has been a significant industry wide increase in R&D expenditure for biosimilar development in India. It amounted to $ 1.4 Bn during the year ended March, 2015, a 28.8% increase from $ 1 Bn in the previous year. [Source: OPPI November 2015]. The increased R&D expenditure is also due to the engagement from the whole spectrum of lifescience companies from large biopharma, major generic companies, young biotech JV ventures and start-ups have who made access and hiring of expertise and skills for biosimilars manufacturing. For example currently there are more than 20 companies developing biosimilars for Trastuzumab, Adalimumab, Rituximab and many such molecules.

Over the last five years, the global technology development landscape for biosimilars reflects not only deeper engagement but also much wider engagement. While the early entrants have the most mature development programs, there have been several late entrants' across Asia, Europe, CIS and Latin America. The current vibrant landscape includes companies across the spectrum of large, mid-sized and smaller ventures. With several active global programs on most emerging biosimilar opportunities, there is far greater possibility today to partner for technology access than there was five years ago. While technology still remains one of the key cornerstones of a sustainable and competitive biosimilar business, its threat as a core barrier to entry is diminishing given the expanded global partnership possibilities.

Frontier efforts: Given the time sensitivity around commercialization of every biosimilar asset, there has been a hard trade-off between optimizing the entire development program and optimizing time to market. With the industry forerunners' programs now coming of age and the overall ecosystem moving beyond nascency, we anticipate that efficient development programs will be set in motion and there will be greater focus on optimizing downstream

processing for higher yields and lowering the manufacturing costs. In addition to innovation in downstream processing, companies could continue exploring alternate expression systems such as plant based platforms in the quest for more efficient and cost effective production processes.

2. Regulatory landscape

The first Biosimilar regulatory framework was launched by the European Medicines Agency (EMA) which came into effect in Europe on October 30, 2005 creating an overarching regulatory pathway for obtaining approvals for biosimilar in the European Union. This subsequently paved path for launch of 21 biosimilar products in EU and many countries adopted the EU principles in their guidelines.

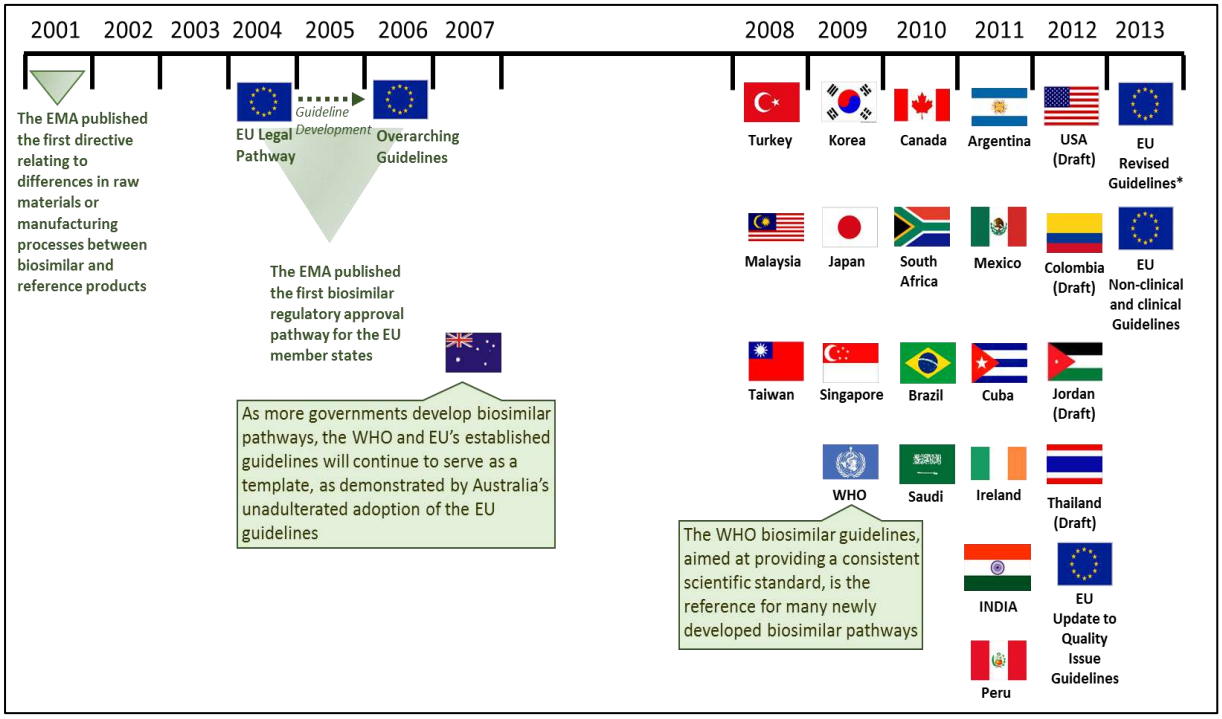


Figure 6: Timelines of biosimilar regulatory guidelines enforcement
Source: http://www.amgenbiosimilars.com/the-basics/how-biosimilars-are-approved/

In the US, a legal framework for approving biosimilars was established in 2009, via the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). Zarxio (filgrastim-sndz) was the first product approved in the US as a biosimilar in 2015 and till date, FDA has approved 4 biosimilars within the product class of granulocyte colony-stimulating factor, a follow-on biological in the product class of insulin for use in the US and two monoclonal antibodies The image above represents the timelines of various countries developing their biosimilar guidelines also represent the timelines for guideline development in these countries.

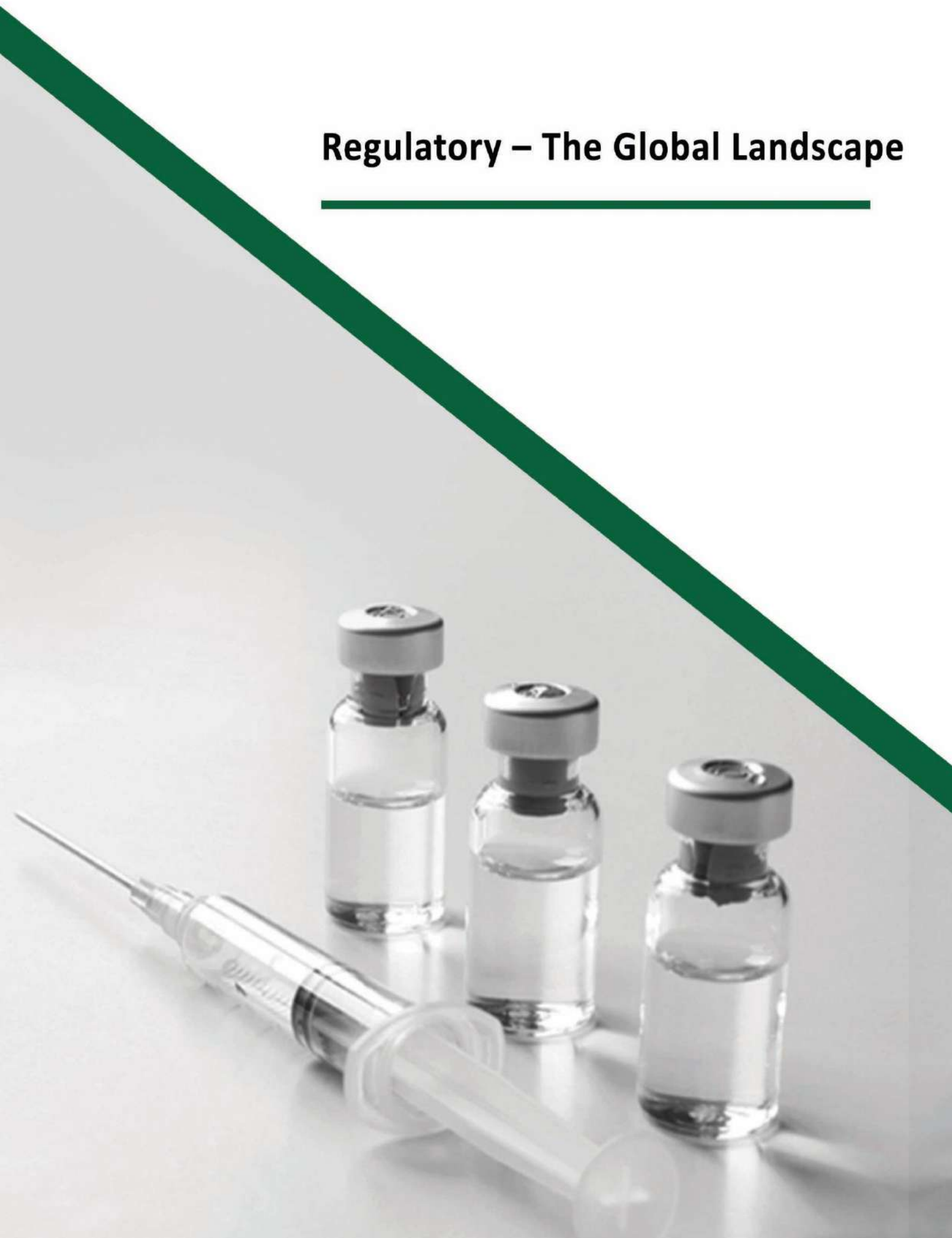
From a regulatory standpoint biosimilars pathways have been defined for most emerging markets with EMA being the forerunner while the regulations are still in flux in China and Russia. Until recently, the FDA has been surprisingly resistant in promoting biosimilars approval, despite BPCIA's instructions to FDA for implementing a framework balancing biologics' and biosimilars' manufacturers' and consumers interests.

3. Market access

While companies are developing greater comfort with technology and regulatory ambiguity is reducing, the next five years will be very critical time period for key market access developments globally. While the overall investment required to develop a biosimilar drug for global markets stands at $100 Mn to $250 Mn, revenues in 2015 were less than $2.5 Bn. Maturity of market access pathways across global regions which includes a clear & robust regulatory pathway and expanded market receptiveness reflected in penetration rates will be critical for demonstrating return on investments and a sustaining industry interest levels over the next decade.

Given the high price of biologic drugs, access has been a challenge in most RoW markets. Biosimilars hold the promise of breaking the affordability barrier and consequently driving market expansion. Such expansion of markets will also be essential to demonstrate a sustainable business case, especially in countries with large out-of-pocket markets. While out-of pockets markets such as India are highly price sensitive, the high power of brands might help contain level of price erosion required to drive such market expansion.

Regulatory – The Global Landscape



IV. Regulatory – The Global Landscape

1. Developed Markets

Europe continues to be the relatively mature region; and market access clarity is now emerging from several European countries with initial monoclonal antibody product adoptions setting the trend. While there has been higher than expected price erosion in certain European markets, this has also resulted in significant share of the innovator drug being gained by the biosimilar within two years from launch (refer discussion in market access section of the white paper). The other developed countries have had a late response to regulatory framework for biosimilars however in the present times with approval of 4 biosimilars in USA (Adalimumab biosimilar has been approved recently) and the current approval of Insulin Glargine biosimilar in Japan, the opportunity in these countries have become more substantial and tangible and we believe with advent of time and the current pipeline of biosimilars the situation will only become better. (Refer to Appendix for more details on approved biosimilars in developed markets).

2. Rest of the World (RoW)

RoW markets remain an important component of any biosimilar asset's strategy given the potential for early revenue streams due to lower regulatory barriers. However, there is no standard prescription and it comprises of countries with a mix of out-of-pocket, payor, capitation and other Government payment models. In the initial five years, exclusive/semi-exclusive partnerships with local entities might be important for market access in several RoW markets given country specific considerations such as PDP framework in Brazil.

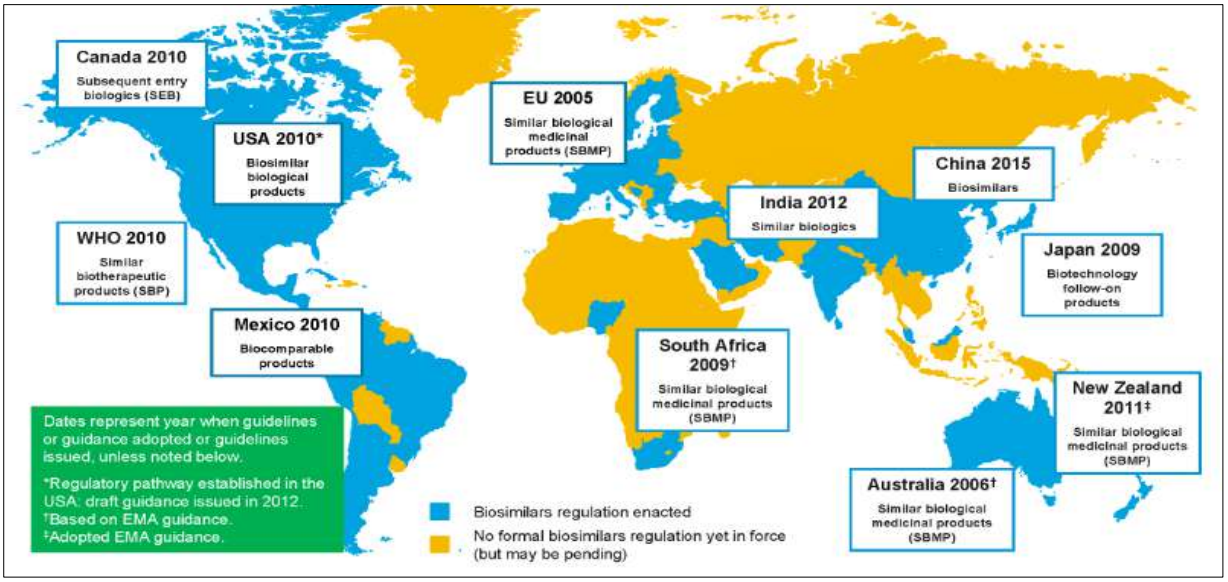


Figure 7: Progression of Clinical Biosimilar Pipeline
Source: Bernstein, Biosimilars: Who is doing what? April 2015

EMA – The Trendsetter

- EMA was early to set up guidelines for biosimilar, which were introduced in **2005**.
- Regulatory Approval typically takes **6-8 years** to reach markets.
- Centralized procedure for all the EU member countries.
- So far **20** biosimilar have been approved in European market.
- Guidelines are laid down categorically. US is also expected to follow same path.
- Interchangeability is handled at country level or pharmacist/physician level.
- No pediatric study/assessment required
- No requirement for any transition studies.
- Biosimilars launch in EU can have the same INN name.

Exclusivity period: 8 years of data exclusivity.
8+2 years of marketing exclusivity.
+1 year marketing exclusivity for second significant new indication during data exclusivity period.
No exclusivity for 1st interchangeable product

USFDA – Opening of Floodgates

- U.S. biosimilar statute became law in 2010 and the FDA's first guidance on biosimilars was released in 2012
- Biosimilar can get approval via abbreviated pathway under section 351(k) of Public Service Act under BPCIA (Biologics Price Competition and Innovation Act of 2009)
- Data package is extensive in case of biologic 351(a) compare to Biosimilar 351(k) but the standards for approval are same.
- So far only 3 Biosimilars are approved in US.
- There were 57 biosimilar and 7 biologic seeking approval from FDA till late 2015.
- Regulatory ambiguity is yet to be broken down with respect to interchangeability.
- Biosimilar label has to specify its relation to reference product.
- Pediatric study/assessment is required if product is biosimilar but not required if product is interchangeable
- Transition study is mandatory for biosimilars.
- Biosimilars launch in US can have the same INN name. However the USFDA have not approved any biosimilar with the same INN name.

Exclusivity period: 4 years of data exclusivity
12 years of marketing exclusivity
1 year of exclusivity period for the 1st interchangeable product

India - Practical and Responsive

Biosimilar guidelines are laid down in 2012

The regulatory bodies responsible for approval of 'similar biologics' in India: Department of Biotechnology (DBT), Review Committee on Genetic Manipulation (RCGM), and the Central Drugs Standard Control Organization (CDSCO)

India has approved 64 biosimilars as of today

Earlier Biosimilars were approved using abbreviated version of pathway by CDSCO and RCGM

There were concerns over scope for different interpretations from the industry. DCGI promised to address them in revised guidelines.

Data exclusivity period was not specified.

New amendments effective from 15th August, 2016:

Robust pre-clinical and clinical data requirements to establish similarity with the reference drug.

Post marketing phase IV studies- which includes a pre-defined single arm study of generally, more than 200 evaluable patients and compared to historical data of the Reference product. The study should be completed preferably within two years of the marketing permission/manufacturing license unless otherwise justified.

With amendments in regulatory pathway Indian regulators are trying to align with global standards and focusing more on patient safety and residual risk of biosimilars.

3. Bird's eye view

With the current emphasis on biosimilars and the economic benefits they promise there has been an increase attention on having a clear and well defined pathway for biosimilars in countries across the world. However the level of stringency varies from country to country and the below picture captures the state of regulatory affairs in these countries.

As would be the case, markets with a mature regulatory pathway has more approved biosimilars as compared to the rest of the world while the countries where the regulatory pathway is less stringent has the largest pipeline of biosimilars awaiting approval as captured in the below figure.

Biosimilars pathway in place	European Union, Malaysia, Singapore, Taiwan, South Korea, Brazil, USA, Japan
Biotech intended copies as new products with less stringent requirements	Indonesia, Thailand, China
Pathway under development	Columbia, Jordan, Venezuela
Similar pathway as a generic product	Vietnam, Philippines, India

Figure 8: Current Biosimilarity pathway
Source: Sathguru's Internal Research

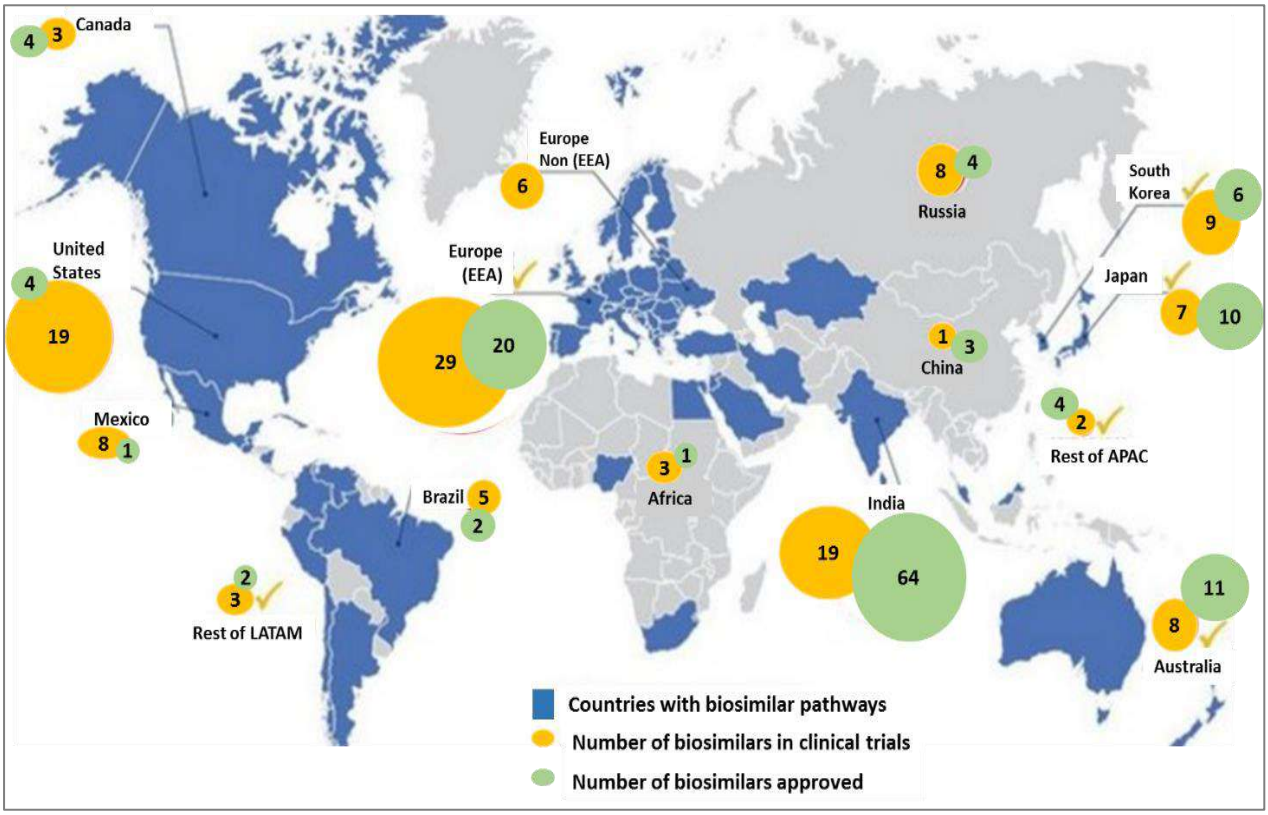
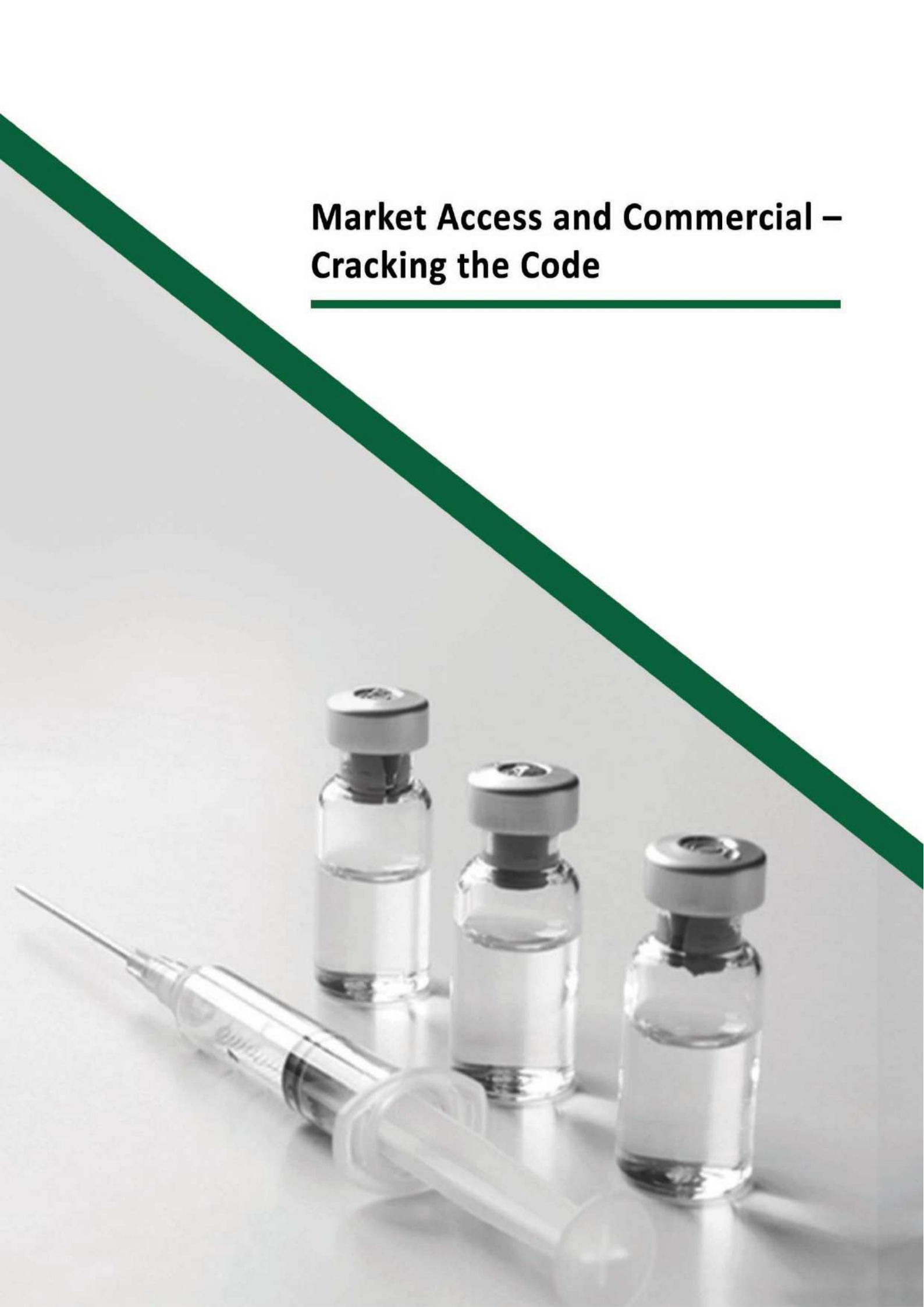


Figure 9: Approved and Pipeline - Biosimilars
Source: Sathguru's Internal Research

Market Access and Commercial – Cracking the Code



V. Market Access and Commercial – Cracking the Code

1. India

Market Size and Competitive landscape

Biosimilars were launched in India during the onset of the millennium 2000; even before they ventured their way into developed markets of US and Europe. Indian industry's engagement has only intensified over the last decade with more than ten companies investing in a pipeline of biosimilar assets. With increasing engagement in the industry, technology expertise has been widening and several large companies have developed expertise in mammalian platforms.

Dense product development engagement and intense competitive landscape – Commercial success during the next five years will be critical for sustained investments and market leadership

Indian Companies Portfolio Snapshot:

Biocon	Biocon has invested $200m in setting up Insulin production plant in Malaysia. Pipeline: Pegfilgrastim, Trastuzumab, Insulin Glargine and Adalimumab
Dr. Reddy's	First Indian firm to rollout a biosimilar, has seen its biologics business grow multiple-fold since the launch of Reditux (rituximab) in 2007 and its products are currently being sold in over 10 emerging markets. Launched: Rituximab, Filgrastim, Pegfilgrastim and Darbepoetin Pipeline: Trastuzumab and Bevacizumab
Reliance Lifesciences	In June 2016, Reliance Lifesciences launched biosimilar of Bevacizumab in Indian market. Earlier in June it entered in exclusive licensing agreement with Torrent Pharmaceuticals for marketing of Rituximab, Adalimumab and Cetuximab
Intas Pharmaceuticals	Intas, which has been selling biosimilars in India and several other emerging markets since 2004, is now starting to focus on the United States and Europe. It launched its first biosimilar Accofil (filgratsim) in Europe in February, 2015.

Zydus	Launched a biosimilar version of adalimumab in December 2014 under the brand name Exemptia. The drug costs one-fifth of the original.
Cipla	Cipla is investing about Rs 600 crore (Rand 1.3 billion) in the new biosimilar manufacturing facility in South Africa, which the company intends to use to serve local as well export markets such as US, Europe and Asia.
Lupin Pharmaceuticals	Lupin formed a joint venture with Japan-based Yoshindo Inc. It is in phase III trial for etanercept and planning to launch it for regulated market.
Torrent Pharma	In January 2016 launched biosimilar for adalimumab with brand name 'Adfrar'.
Hetero Pharma	In June 2016 rolled out biosimilars for bevacizumab with brand name Cizumab, earlier launched Darbepoetin alfa and Rituximab
Aurobindo	Announced foray into biosimilars.
Alkem Laboratories	Acquired Enzene, a company engaged in the development of biosimilars in India.
Emcure	Partnered with Roche to sell biosimilars of Herceptin and Rituximab
IPCA Labs	Entered into a partnership with US-based Oncobiologics Inc for producing mAbs.
Wockhardt	Launched Wepox (recombinant human erythropoietin), Wosulin (recombinant human insulin) and Glaritus (long-acting Insulin Glargine) in India

Additionally, small to mid-sized companies continue to engage in products using the microbial platform or only APIs. The Indian landscape also includes some promising startups but their efforts have been slowed down by the challenge of access to scale-up capital during the product development phase.

As a first step, most Indian companies are focused on commercializing their biosimilar pipelines in India to be followed by other RoW markets in the near term. The commercial attractiveness of the biosimilar segment in India will be an important consideration for sustained investments by the industry.

Facilitating access- Breaking the affordability barrier

While novel biologics approved in the last ten years have been addressing several critical unmet needs in healthcare, penetration of biologics has been skewed towards the developed world as compared to developing nations, as depicted below:

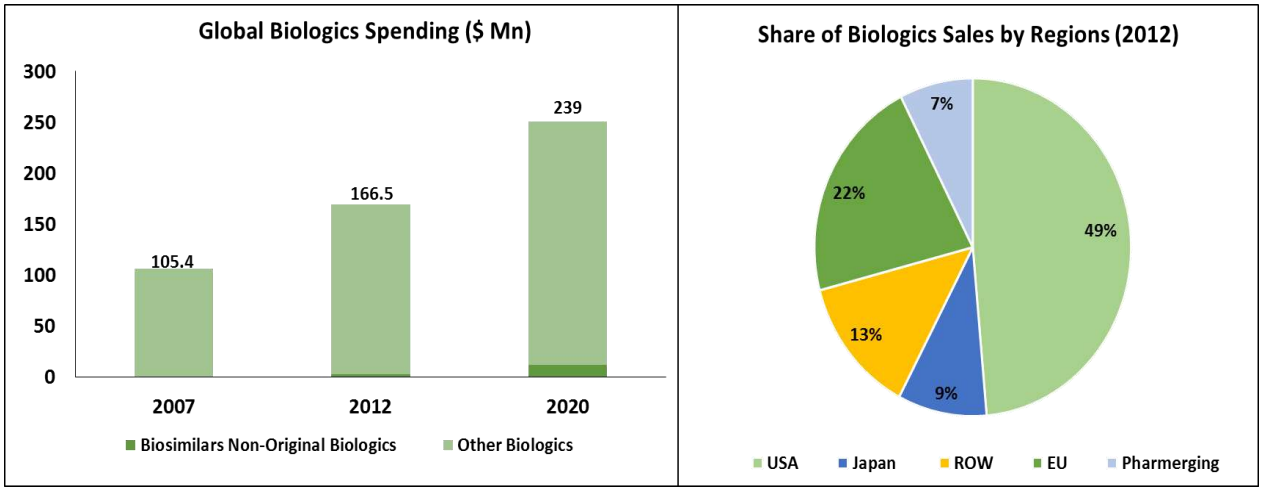


Figure 10: Global Biologics Spending and Biologics share of sales by region
Source: IMS Health, MDAS, December 2012

The exorbitant cost of biologic treatment has been a hindrance to widespread adoption in most emerging markets. Biosimilars hold the promise of addressing this affordability challenge and thereby facilitating access to large patient pool in emerging markets such as India. This expansive unmet need is the largest market driver in India and other RoW markets.

Price erosion benchmarks evolving

As price sensitive markets with significant unmet need, competitive pricing will be important to expand presence in the Indian market. However, this propensity to lower price in a quest to expand markets is balanced by two factors:

1. **Brand power –** As a sales driven branded generics market, companies are likely to use brand power to avoid accelerated price erosion for their biosimilar assets.
2. **Missing inverse correlation –** As discussed subsequently, market expansion observed with availability of lower cost biosimilars is not very encouraging and price reduction may not on its own lead to maximizing penetration potential.

Table depicting price erosion of biosimilars in India, Source: IMS Report

Price in India for same quantity	Price Erosion (2015 / Year before launch of biosimilar)
Abciximab	59%
Etanercept	61%
Rituximab	50%

Adalimumab	80%
Pegfilgrastim	73%

In summary, affordability of biosimilars will be important for growth in India and other RoW markets. However, given the complex dynamics around market expansion, we believe that price erosion in these markets will not be greater than what has been observed in Europe. Current examples from Europe will continue to set the threshold for price erosion across global markets.

At present, there are as many as 27 biosimilar manufacturers in India one of the major challenges facing the Indian biosimilar industry is ongoing questions surrounding product quality and safety.

The market expansion imperative

Given the early product launches in India, market penetration data can be analyzed for a longer period as compared to markets in developed countries. Until now, market expansion in India and growth for the biosimilar assets launched has been, at best, lukewarm. While the CAGR might be encouraging, the absolute size of the market is relatively small considering the negligible base and expanse of unmet need in India. Biosimilars launched offer potential of breaking the affordability barrier for marketed biologics that are beyond the reach of majority of Indians and hence expanding markets by a very high multiple. However, current market penetration is far from such potential.

The current market landscape calls for all stakeholders (Government, policymakers and regulators, clinical associations, patient support groups and industry) to join forces and push the boundaries of biosimilars adoption to realize the potential for the benefit of both industry and the patient. Countries like Norway provide great examples of engaging the clinical community in decision making and fostering greater adoption of biosimilar. Driving market expansion also calls for a collaborative effort from industry players as compared to the current strategy of going solo to market. Indian industry itself provides great examples such in the case the DPP4 inhibitors for type 2 diabetes where marketing collaborations have been beneficially deployed to accelerate growth and product penetration.

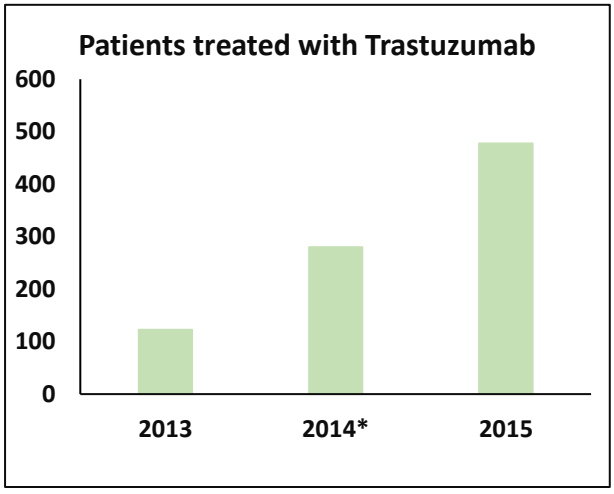


Figure 11: Patients treated by Trastuzumab
* Biosimilar launched in 2014

Indian market – way forward

The Indian market for biosimilars is intensely competitive and will continue to be so. While the number of Indian companies that finally establish a foothold in developed markets will only be few, we anticipate that the Indian market itself will continue to have many players including several international companies marketing products in India through collaborations. We would like to highlight the urgent need to focus on the most important commercial element – market expansion. As a fragmented out-of-pocket market where the final beneficiary 'the patient' has little voice, it is critical companies engage in collaborative efforts to jointly accomplish this feat. The Indian biosimilar segment has been replete with collaborations for product development – as we step into the next era of biosimilar opportunity in India, companies should now extend the same focus on collaborations to the market end.

2. Regulated Markets

According to IMS health study, total value of Biosimilars opportunity in US and EU nations in 2015 with eight top-selling biologics on patent cliff between 2015 and 2020 was $47 Bn.

EU market	US market
EU is considered to be most matured market with 80% of the global biosimilar spending	The U.S. has taken a more cautious pace for the approval of biosimilars than the EU took in its first few years
Early adopters : Over the past ten years, the EMA has approved 21 biosimilars under the guidelines	In March 2015 Sandoz's Zarxio (filgrastim) was approved in the United States as a first biosimilar by FDA. Pfizer's Inflectra (in April 2016) and Eli Lilly's Basaglar (Jan 2016) are recent approvals.
Adoption in European market is uneven mainly because of country specific substitution policies although EMA remains as central authority for entering EU market	U.S. biosimilar statute became law in 2010 and the FDA's first guidance on biosimilars was released in 2012. Regulatory ambiguity delayed launch of biosimilars in US. The USFDA 2016 approvals are symbolic and herald opening of the world's largest market.

In Europe, biosimilars are generally referred to by their trade names	FDA issued new guidelines which requires the addition of a randomly-assigned suffix for all biologic products
29 Products in Pipeline	19 Products in pipeline

Given the forthcoming regulatory environment in Europe, within the developed markets, the EU has both a denser portfolio of approved and marketed biosimilars as well as more clarity on market access. Please refer to Appendix for the approved list of biosimilars in Europe.

While several European companies were engaged in development and commercialization of the microbial products, only a few large multinationals are currently advancing monoclonal antibodies to market in US and EU. This concentration of pipeline in few large companies has been largely due to the level of investment required for clinical validation as well as the current level of risk emanating from evolving regulatory and market access considerations.

With international companies like Celltrion having partnered with local entities in Europe for market access, now several other companies have developed comfort with biosimilar markets as well as understanding of the market access. These companies are now developing proprietary biosimilar portfolios to leverage the market access knowledge and build a sustainable presence in the segment. With this dynamic, the biosimilar engagement in Europe is gradually expanding beyond the few multinationals and next five years will witness the emergence of several small to mid-sized European companies with proprietary/partnered portfolios.

i. Substitutability still evolving

As biological drugs are derived from living cells, which have natural variations, biosimilars can never be exact copies and policy frameworks on substitutability are evolving in most parts of the world. Final position on substitutability in each region has direct impact on the following considerations:

1. Automatic substitution of originator with biosimilars
2. Switching of originator drug with biosimilar drug and vice versa
3. Naming of biosimilar drugs

While the first two considerations are critical for market penetration and accelerated adoption of biosimilars across markets, the last consideration significantly impacts the marketing approach and marketing expenditure.

EU: Automatic substitution does not yet prevail in EU for any approved biosimilar. EMA, per its revision of the 2005 guidelines, leaves the decision on interchangeability to the EU Member States giving the approval. We notice varying levels of adoption across countries in

EU and interchangeability has not been a barrier to high market penetration rates in countries that have been supporting of biosimilars to drive down Healthcare costs and expand healthcare access.

US: While the BPCI Act states that interchangeable biologics may be substituted without the intervention of the healthcare provider, the regulatory perspective on substitutability is nascent with USFDA still establishing the standards for interchangeability. While the USFDA has released draft guidelines on non-proprietary naming of biosimilars and labeling of biosimilars, final interchangeability guidance is expected by the end of 2016. State regulations in the US vary as well with a total of 36 states having considered legislation for substitution of original biologics by biosimilars.

Substitutability currently remains uncertain in US and serves as a deterrent to several potential industry players who are concerned about the pace of evolving maturity in policy frameworks. However, the 2016 USFDA biosimilar approvals set a positive tone on the regulatory front and we perceive them as a precursor to greater clarity on market access considerations. Particularly, the favorable recommendations on extrapolation of indications is encouraging and reflects regulators' comfort progressing in the direction of interchangeability.

ii. Broken myth of 20% price erosion

Biosimilars have always been pitted as the royal kin to the commoner, the small molecule generic. This perceived supremacy and commercial attractiveness of the biosimilar segment was heavily based on the expectation of minimal price erosion. Due to the molecular complexity, high production costs and relatively high barriers to entry, it was expected that biosimilar prices would hover at around 20% below the innovator drug price. However, experience across biosimilar launches in EU emphatically scream that this myth has been shattered.

Price erosion (2015/The year before biosimilar entrance)	**EPO**	**G-CSF**	**HGH**	**Anti-TNF**
Norway	48%	56%	23%	48%
Czech Republic	47%	28%	16%	16%
Finland	42%	31%	28%	10%
Hungary	55%	53%	2%	7%
Ireland	35%	24%	11%	1%
Slovakia	60%	79%	10%	6%
Romania	51%	51%	12%	12%

Portugal	71%	87%	33%	20%
Germany	53%	30%	-3%	4%
Italy	11%	24%	17%	1%

Source: IMS Report

In Europe, the initial biosimilars launched in the areas of growth hormones, blood cell modifiers were introduced with varying discounts and success. However contrary to initial market expectations, some recent cases on the observed in Europe with respect to Filgrastim, Epoetin Alfa, Rituximab and several other drugs indicate a greater price erosion of upto 70-80% roughly six months after loss of exclusivity, particularly as competition increased. Table above depicts the reduced average price of GCSF in Europe over the years since its launch in Europe with the growth rate of the drug.

These discounted of prices of the biosimilars also help in larger market penetration of these drugs such as observed in the case of Remimsa with a market dominance in Norway by Orion Pharma with their aggressive pricing of 69% discount on J&J's Remicade. The market volume of Remicade varied within the European based on the price erosions as depicted in the table above.

3. Other Global Regions

Korea:

The Korean biopharmaceutical industry is a fast evolving one with a huge potential in domestic as well as export markets. The domestic biopharmaceutical sales stood around ~$3 Bn in 2013 and is growing at a CAGR of ~6%. Korea was also an early adopter of Biosimilar regulations (the Korean regulations are similar to EMA) and has approved 6 biosimilars till date:

Along with this Korean biopharmaceutical companies have actively sought partnerships with global pharmaceutical companies such as:

a. Hanwha Chemical entered in agreement with Merck to globally market Enbrel® biosimilar
b. Samsung Biologics established a joint venture with Biogen to manufacture biosimilars
c. Celltrion and Pfizer to manufacture and market Remicade® biosimilar

Apart from the above advances made by the above mentioned private players Korean government is also giving a boost to Biopharmaceutical sector and has launched a fund worth $90 Mn. Korean players have already gained early inroads in the EU and US biosimilars' market with Celltrion gaining approval for Infliximab biosimilars in 2013. The list of approved biosimilars of Korean origin is listed in the adjacent table:

Biosimilar	Approval Date	Name of Company
Etanercept	8-Sep-15	Samsung Bioepis
Etanercept	11-Nov-14	Hanwha Chemical
Trastuzumab	15-Jan-14	Celltrion
Somatropin	Jan-14	Sandoz
Infliximab	23-Jun-12	Celltrion
Infliximab	4-Dec-15	Samsung Bioepis

Note: Celltrion has ~32% of market share by volume of Infliximab market.

Source: IMS MAT Mar'15 Data

Korean biosimilars market will be difficult to break in for Indian companies given high level of domestic competition in Korea. While Celltrion is the forerunner to global markets, engagement within Korea has widened and several companies are making significant investments. The Korean industry is poised for global success in the biosimilars segment and could provide strong competition to companies from both developed as well as RoW countries.

LATAM:

The LATAM market for Biosimilars is set to grow owing to the government's push for biosimilars in order to decrease the total cost of healthcare budget. The total market value was $123Mn in 2013 and is expected to grow at a CAGR of ~38% for the next decade and presents a very lucrative opportunity for interested players in this field.

However, the regulations for Biosimilars in these countries is quite stringent and creates a high entry barrier for companies entering the market. A comparison of the regulatory pathways in these countries is summarized in the table below:

BRAZIL		ARGENTINA	CHILE	MEXICO	VENEZUELA
Comparability Pathway	Individual Development Pathway				
Highly stringent Comparability study with	Less stringent but extrapolation	Comparability study with originator. Extrapolation	Required as for new drug.	Required as for new drug.	Required as for new drug.

originator. Extrapolation of indications is allowed	of indications not allowed	of indications is not allowed	Extrapolation of indications is not allowed	Extrapolation of indications is not allowed	Extrapolation of indications is not allowed

Apart from this the local government in some countries have mandated that the production of drugs happen locally and others have put a high duty for imported products. These conditions combined create a very high entry barrier for these highly lucrative markets.

Currently as the entry barrier is high and there is significant risk in developing these molecules, several local companies have formed a consortium to participate in this sizeable market. For e.g.

a. Orygen, a JV between Eurofaarma and Biolab has signed PDP agreement with Brazilian government for Adalimumab, Etanercept and Bevacizumab
b. Bionovis, a JV between EMS, Uniao Quimica, Hypermarcus and Ache Labs has signed PDP agreement with Brazilian government for Bevacizumab, Infliximab, Etanercept & Trastuzumab

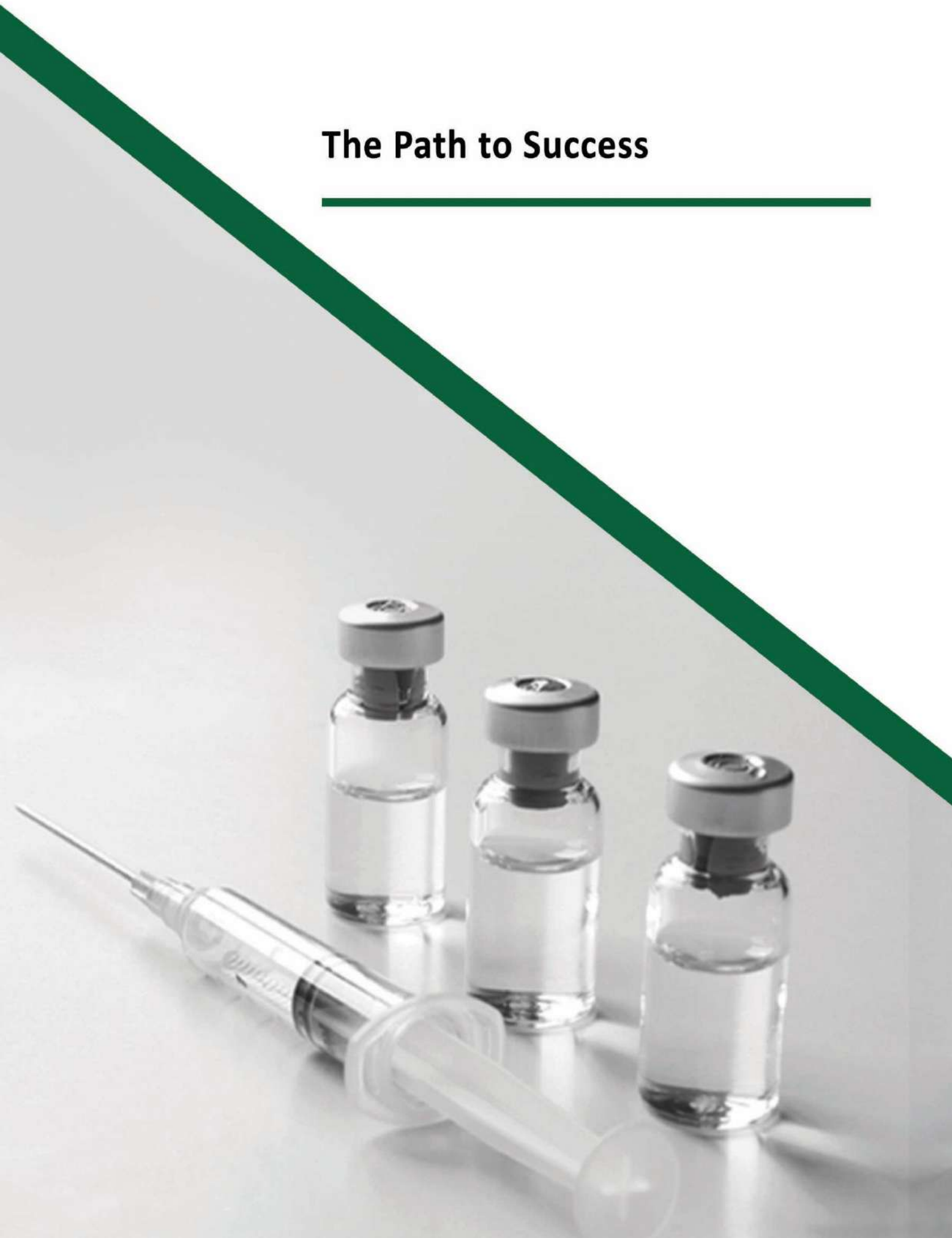
Historically there hasn't been an active biosimilar product development landscape in the Latin American region and these joint ventures and few large local players such as Libbs have partnered with leading MNCs to gain the technological knowhow to manufacture the biosimilars locally and tap into the large domestic market. This is rapidly changing with several of the local companies/consortia now engaging in pipeline development through internal efforts.

Low maturity of local product development engagement creates significant opportunity for Indian firms to partner with Latin American companies to reach these attractive markets. There is already history of partnership between Indian and Brazilian firms for small molecules and these could be synergistically emulated for biosimilars as well.

Russia

Like many other emerging countries in the world, Russia's reliance on high-priced foreign biologics is growing and is causing an enormous financial strain on the country's nationalized healthcare system. Interestingly, despite the lack of a defined regulatory approval process, biosimilar versions of EPO and G-CSF are currently commercially available in Russia. Biocad is the major biosimilar manufacturer in Russia and currently sells biosimilar versions of EPO, G-CSF, and interferon-beta-1a as a multiple sclerosis treatment. Despite the relative immaturity of the Russian biosimilar industry, Russia is poised for expansive growth in this area.

The Path to Success



VI. The Path to Success

The biosimilar segment is hard to ignore for both innovative biologic companies as well as small molecule generic companies. With the tectonic shift to biologics as the growing source of therapeutic solutions and the global quest for affordability, biosimilars are commercially very attractive. However, the path to success is still elusive and ambiguous. We discuss below the critical challenges in the current landscape.

1. Critical Challenges

a) Optimizing technology strength

While the global biopharmaceutical industry has made significant progress in mastering the complex technology behind manufacturing a biosimilar, it still remains a very important cog in the wheel. With a number of Indian companies having frayed into the biosimilar segment, the barrier from a technological standpoint has significantly come down. However, it will continue to remain an important consideration for any newcomer trying to enter this segment. Despite strong internal programs, even existing players might seek technology access for individual molecules as a means of accelerating time to market. In the next five years, it is also critical that companies strengthen their understanding of analytical validation required and internal clinical development required. This will be a key determinant of success in various global markets. Finally, technology challenge will now evolve beyond developing a biosimilar molecule that is a fingerprint copy of the original, to achieving greater optimization of processes and costs without compromising time to market.

b) Winning the race of time to market

In the quest for RoI, time to market remains the most important driver of success in the current biosimilar landscape.

Market size of innovator molecule ($ Mn)	**2,000**	**5,000**	**10,000**
Case -1			
Price erosion %	40%		
Size of biosimilar market ($ Mn)	1200	3000	6000
Number of Players	5		
Market share of each biosimilar company	240	600	1200
Case -2			
Price erosion %	60%		
Size of biosimilar market	800	2000	4000
Number of Players	5		
Market share of each biosimilar company	160	400	800
Case -3			
Price erosion %	80%		
Size of biosimilar market	400	1000	2000
Number of Players	5		
Market share of each biosimilar company	80	200	400

Early winners club in developed markets – The cost of development for US and Europe is north of $ 100 Mn per molecule and ranges between $ 150 Mn to $ 200 Mn. Market size of the biosimilar market when there are more than 5 players per molecule in the developed markets does not provide financial viability to recover this high level of investment that carries binary risk. Hence, the biosimilar competitive landscape will be dominated by the early winners in each molecule. With no anticipated near term decline in the level of investment required and steeper than expected price decline being observed in various European markets, this criticality of time to market as a key determinant of biosimilar success will only increase in the near future.

Moreover, as discussed earlier in our white paper, biosimilar assets launched in several geographic markets reflect a steep price decline during the first two to three years after launch. Hence, the time to market also becomes important to skim the market when the prices are more attractive and early entrants for every molecule will continue to have an advantage. Biosimilar assets launched in several geographic markets reflect a steep price decline during the first two to three years after launch along with a substantial rise in volume uptake thereby increasing the revenue and offsetting the setback of price erosion. However once the market matures there is limited volume expansion even if the price reduces substantially. Hence, the time to market also becomes important to skim the market when the prices are more attractive and early entrants for every molecule will continue to have an advantage. The table below shows the data for two such biosimilars, one mature and other new:

G-CSF in EU Countries (Mature Product); Source: IMS MAT Mar'15 Data

G-CSF	Price Evolution		Volume Evolution		Biosimilar Launch Year
Country	2014/the year before biosimilar launch	2015/the year before biosimilar launch	2014/the year before biosimilar launch	2015/the year before biosimilar launch	
Germany	-6%	-30%	43%	54%	2008
Finland	-12%	-31%	48%	61%	2009

Infliximab in EU Countries (New Product); Source: IMS MAT Mar'16 Data

Infliximab	Price Evolution		Volume Evolution		Biosimilar Launch Year
Country	2014/the year before biosimilar launch	2015/the year before biosimilar launch	2014/the year before biosimilar launch	2015/the year before biosimilar launch	
Norway	-3%	-48%	13%	51%	2013
Portugal	-12%	-20%	16%	33%	2013

At the current pedestal, the companies that are closer to success are the ones that have aced the race to be first to market and are part of the early winners' club. Several robust biosimilar programs across geographies are seeing sunk investments eroding in value on account of delays in commercialization. The last five years hold out several lessons for biosimilar success and companies are now more actively vigilant about balancing program robustness and time to market.

c) Shouldering level of investment and binary risk

The quantum of investment required for a biosimilar development is **twenty to hundred times** the investment required for a small molecule generic (considering $1 -5 Mn for a small molecule generic and north of $150 Mn for a biosimilar). If a company builds a portfolio of about five biosimilar molecules for the developed markets, the minimum investment required is in the range of $600Mn to a $1Bn. Almost the entire quantum of investment carries binary risk. Size of the investment required and related risk has proven to be the largest deterrent, especially for success in US and Europe.

While all the factors mentioned above apply to global markets overall, the risks associated with investment are lower in case of RoW markets as the regulatory pathway is relatively easier to traverse and quantum of investment is lower. However, as of now, the market expansion/uptake of biosimilars in these markets have been very slow and standalone financial viability for sustained investments is questionable until the commercial forces are remedied.

d) Balancing risk and winning amidst uncertainty

The global biosimilar opportunity is becoming more tangible with USFDA turning forthcoming with approvals and biosimilar penetration stories emerging from across the world. However, challenges discussed above continue to loom over Indian industry. The current crossroads call for the industry to evolve winning strategies to chart the course to global success.

2. Recommendations

We present below final recommendations for industry and policy makers:

a) Survival of the most collaborative – The partnership imperative

Majority of current challenges stem from commercial considerations and the criticality of time to market and risks associated with quantum of investments required. While these challenges are hard to conquer for most mid-sized companies, the challenges begin to ease out when the prescription of collaboration is practiced. We believe that the mantra in the biosimilars segment will be 'survival of the most collaborative'. Partnering is not an option but a critical means to success in the biosimilar segment. Especially given the glaring reality

of sunk investments in robust standalone programs, synergistic and risk sharing partnerships can expand the horizon of success for industry as a whole:

i. Technology and acceleration advantage:

Collaborations across range of technology focused partnerships will provide the advantage of pooling technology prowess to accelerate development efforts as well as expand the pipeline of assets. As emphasized above, time is the largest value driver in the biosimilars segment and collaborations for technology access and product advancement will allow Indian companies to commercialize products sooner than they can get going completely on their own. While Indian companies have been open to technology collaborations, there is significant scope to more effective engagement in such partnerships to provide the much needed acceleration advantage required for success.

ii. Breaking the Goliath vs Goliath phenomenon - defraying clinical validation risk and breaking into the lucrative regulated markets:

As discussed above, the quantum of investment required to foray into developed markets is a deterrent for most mid-sized companies. The minimum portfolio investment and binary risk of $600Mn to $1Bn has led to the Goliath vs Goliath challenge in regulated markets. Analysis of late stage pipeline (ongoing or completed Phase III or approved) in US and EU reflects a dominance of innovator drug companies in biosimilar pipelines with a small exception of couple of standalone biosimilar companies such as Celltrion from Korea. Largely, it is the same small pool of innovator drug companies that are also advancing the biosimilar assets to market in the highest value markets of the world and holding the rope at both ends – novel biologics as well as biosimilars.

Collaborations present the most promising solution for Indian companies to break-in to regulated markets in the near term and participate in the larger global opportunity. The $1B binary risk per portfolio of biosimilar assets becomes surmountable when shared amongst a group of collaborators and will allow Indian players to break the dominance of a handful of companies in global markets. Co-investment collaborations can thus make risk palatable as well as accelerate market access across various global markets.

Successful co-development partnership for global commercialization of biosimilars
Biocon-Mylan: 6 biosimilars and 3 insulin analogues to access global markets – Trastuzumab and Pegfilgrastims accepted for marketing authorization review by EMA
Adalimumab and insulin analogues ongoing global phase 3 clinical trials
Biocon-Fujifilm: insulin glargine co-development for Japan – Launched in 2016

Models of collaboration could span across partnering with regulated market companies with appetite to share investments and risks, with RoW market companies for local validation investments and market access experience as well as pure Indian consortiums

where a group of Indian companies can share risks and propel the industry to regulated market success.

There is currently a dearth of partnerships amongst Indian companies with the exception of one unannounced co-validation investment for an oncology monoclonal antibody asset for the Indian market. Industry consortium examples from Brazil where leading Brazilian pharmaceutical companies have pooled efforts to participate in the biosimilars opportunity. Compared to partnerships for technology, Indian companies have been less active in forging product advancement or commercial partnerships. To progress to a globally recognizable level of success, Indian industry ought to be more enthusiastic collaborators. Leveraging co-investment collaborations that defray risks and accelerate path to markets will be critical to translate current level of active engagement in Indian industry to a significant share of the $240 Bn opportunity in 2030.

iii. Expanding India & RoW Markets:

The RoW markets are the near term focus of Indian and other emerging market companies. They present lower barriers to entry but given industry experience so far, they have also taken longer to access and penetrate. Market access considerations vary across the wide spectrum of RoW markets and market expansion until now has been less encouraging in most of the countries.

We believe that accelerating market expansion will be the largest determinant of success in RoW markets. It is very important that industry as a whole drives such market expansion to finally build a sustainable and financially rewarding mid to long term engagement in the RoW markets. Near term financial viability also rests on the premise of market expansion.

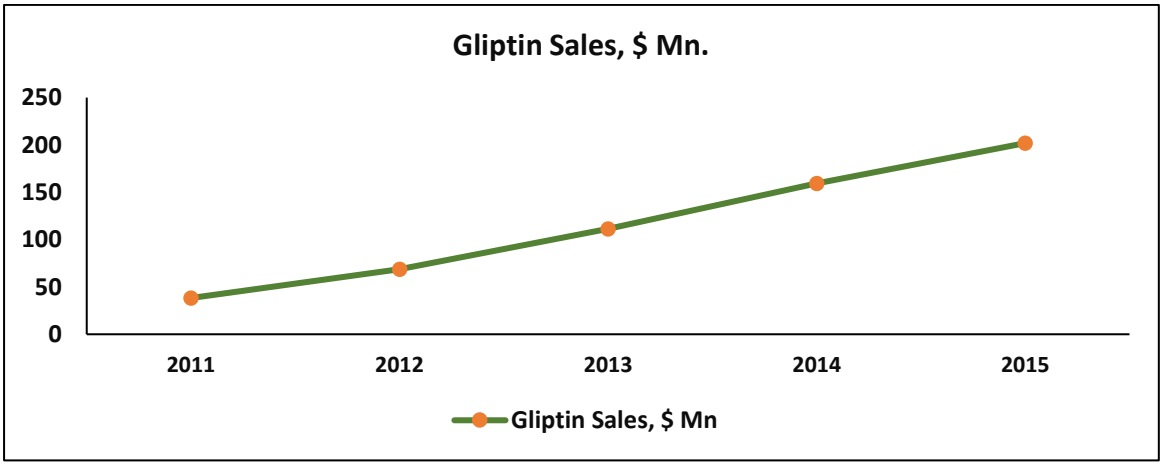


Figure 12: Gliptins Sales- India
Source: IMS data, MAT March

In out-of-pocket markets like India, industry collaborations can again play a critical role in creating financial viability by expanding markets to their potential. In such out-of-pocket markets, commercial and marketing partnerships will lead to greater momentum in the

education of stakeholders and accelerating product adoption. Picking a leaf from the small molecules, the growth of gliptins (DPP4 inhibitors) as an accepted therapy in the Indian market was largely led by multiple marketing collaborations between MNCs and Indian companies and establishes the potential of market creation partnerships. Indian companies are already deeply invested in biosimilars for RoW markets and commercially focused partnerships can now propel them to the next era of success and financial rewards.

b) Policy and regulatory measures

In addition to industry led collaborations and acceleration efforts, the following policy measures can provide the required impetus for domestic firms to succeed in global markets:

i. Higher quantum of non-dilutive funding for development:

As discussed above, the quantum of clinical validation investments for developed markets and related risks continue to be a challenge even for large Indian companies. While quantum of investments is manageable for large companies focused on India and other RoW markets, younger technology driven companies from India have experienced value erosion with paucity of risk capital for clinical validation of biopharmaceutical products.

While India does have non-dilutive grant funding opportunities for initial de-risking of technology, the quantum of such funding is negligible given the long path of biosimilar product development and validation. While current non-dilutive funding mechanisms from Indian Government can support young ventures in the first few steps of development, a well-structured funding to de-risk the most capital intensive step of clinical validation for global markets could truly be instrumental in Indian industry carving global presence in biosimilars. To be truly impactful, such funding mechanism needs to be of sizeable quantum and take cognizance of time sensitivity of the biosimilar commercialization process.

The Korean government's $90 Mn Korea Drug Development Fund has been instrumental in fueling the country's pipeline and trigger sustainable drug discovery and development engagement in the biopharmaceutical sector. Similarly, non-dilutive funding support from the Indian Government can seed sustainable engagement in the segment by de-risking initial portfolio building and laying the foundation for sustainable investments in the segment.

ii. Technology acquisition fund

Technology continues to be a foundational element for success in biosimilars. As highlighted earlier, while several Indian companies have now built strengths across microbial and mammalian technology platform, technology access at the asset level will be important for accelerating path to markets. Again, current non-dilutive funding mechanism from the Government do not fund technology acquisition. Technology acquisition are the starting points of risk investments made by companies and we recommend that de-risking support to be extended to the point of technology acquisition. Even current fiscal incentives are limited to in-house research and development and revenue from out-licensing of patents. To equip the Indian biosimilar industry to be globally competitive, it is critical that such fiscal incentives be extended to corporate investments in technology acquisition.

iii. Ease of regulatory approvals:

The Indian regulator has been one of the forerunners in the RoW landscape to formally roll out biosimilar guidelines and has even revised the guidelines more recently to make it more consistent with global approval pathways. Industry has largely heralded the Indian biosimilar guidelines as pragmatic while ensuring the required bar on safety is maintained and patient interests are upheld.

However, there is great need for fine-tuning regulatory processes overall to facilitate ease of functioning. Both biosimilar product companies and CMOs have indicated need to drop several non-consequential procedural steps such as approvals for toxicology studies, approvals for clone development/import, approval for CMOs to manufacture clinical trial material etc. Especially, given the time sensitivity of the biosimilar development process, ease of traversing the regulatory pathway and simplicity of procedures will be fundamental to competitiveness of CMOs as well as companies with proprietary biosimilar pipelines and needs urgent attention.

iv. Fiscal incentives:

India has attracted negligible component of MNC investments in biologics manufacturing infrastructure. Several global destinations such as Switzerland, Ireland, China, Singapore, Malaysia etc are emerging as more attractive investment destinations primarily due to fiscal incentives. For e.g. Malaysian and Thai governments are creating biotechnology parks that provide tax holidays on the investments in manufacturing infrastructure, thereby attracting global industry investments.

The momentum in the biosimilar segment is ripe at the moment and globally competitive fiscal incentives will allow India to participate in this global opportunity. In addition to encouraging manufacturing investments in line with India's Make in India program, the Government should also consider fiscal incentives to incentivize Indian industry to make the next leap in biosimilar investment and engage in more aggressive product development as well as global commercialization programs. Indian biosimilar industry now has a vibrant level of engagement to benefit from such incentives and move to a globally commanding presence. This progression is a capital and risk intensive effort and calls for a high level of Government support.

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Abbreviations

Abbott	Abbott Laboratories
Alkem	Alkem Laboratories Pvt. Ltd.
Aurbindo	Aurobindo Pharma Ltd.
Aventis	Aventis Pharma Ltd.
Bharat Serum	Bharat Serums And Vaccines Ltd.
Biocon	Biocon Limited
Bn	Billion
BPCI	Biologics Price Competition and Innovation
CAGR	compunded Annual Growth Rate
CDSCO	Central Drugs Standard Control Organization
Cipla	Cipla Pharmaceuticals Ltd.
CIS	The Commonwealth of Independent States
Corona	Corona Remedies Pvt. Ltd.
DBT	Department of Biotechnology
DCGI	Drug Controller General of India
DPP-4	Dipeptidyl peptidase-4 inhibitor
DRL	Dr. Reddy's Laboratories Ltd.
EMA	European Medicines Agency
Emcure	Emcure Pharmaceuticals Ltd.
EPO	Erythropoietin
EU	European Union
FDA	Food and Drug Administration
G-CSF	Granulocyte-colony stimulating factor
Hetero	Hetero Drugs Ltd.
HGH	Human Growth Hormone
Intas	Intas Pharmaceuticals Ltd.
Ipca	Ipca Laboratories
LG	LG Life Sciences
Lupin	Lupin Ltd.
mabs	Monoclonal Antibodies
Mn	Million
MSD	Merck & Co., Inc.
Mylan	Mylan N.V.
NBE	New Biologic Entity
OPPI	Organization of PharmaceuticalProducers of India
PDP	Productive Development Partnerships
R & D	Research and Development
RCGM	Review Committee on Generic Manipulation
RLS	Reliance Life Sciences Pvt. Ltd
ROI	Return on Investment

ROW	Rest of the World
Rs.	Indian National Rupee
SBMP	Similar Biological Medicinal Products
SBP	Similar Biotherapeutic Products
SEB	Subsequent Entry Biologics
TNF	Tumor necrosis factor
WHO	World Health Organization
Wockhardt	Wockhardt Ltd.
Zydus	Zydus Cadila Healthcare

Appendix

EMA approved Biosimilars as on Sept, 2016

Biosimilar Trade Name	Marketer	Active Substance	Reference Drug	Year of Approval
Epoteins				
Abseamed	Medice	epoetin alfa	Eprex/Erypo	2007
Binocrit	Sandoz	epoetin alfa	Eprex/Erypo	2007
Epoetin Alfa Hexal	Hexal	epoetin alfa	Eprex/Erypo	2007
Retacrit (2)	Hospira	epoetin zeta	Eprex/Erypo	2007
Silapo	Stada	epoetin zeta	Eprex/Erypo	2007
Filgrastims				
Accofil	Accord	filgrastim	Neupogen	2014
Biograstim	AbZ-Pharma	filgrastim	Neupogen	2008
Filgrastim Hexal	Hexal	filgrastim	Neupogen	2009
Grastofil	Apotex	filgrastim	Neupogen	2013
Nivestim	Hospira	filgrastim	Neupogen	2010
Ratiograstim (withdrawn)	Ratiopharm	filgrastim	Neupogen	2008
Tevagrastim	Teva	filgrastim	Neupogen	2008
Zarzio (3)	Sandoz	filgrastim	Neupogen	2009
Follitropins				
Bemfola	Finox	follitropin alfa	GONAL-f	2014
Ovaleap	Teva	follitropin alfa	GONAL-f	2013
Growth Hormones				
Omnitrope (4)	Sandoz	somatropin	Genotropin	2006
Insulins				
Abasaglar (5)	Eli Lilly	insulin glargine	Lantus	2014
Monoclonal Antibodies				
Inflectra	Hospira	Infliximab	Remicade	2013
Remsima	Celltrion	Infliximab	Remicade	2013
Flixabi	Samsung Bioepis	Infliximab	Remicade	2016
Dimeric fusion protein				
Benepali	Samsung Bioepis	Etanercept	Enbrel	2016

USFDA approved Biosimilars as on Sept, 2016

Biosimilar (Manufacturer)	Biologic (Manufacturer)	Biosimilar Code Name	FDA Approval Date
Zarxio® (Sandoz)	Neupogen® (Amgen)	Filgrastim-sndz	March 6, 2015
Inflectra® (Pfizer)	Remicade® (Johnson & Johnson)	Infliximab-dyyb	April 5, 2016
Erelzi® (Sandoz)	Enbrel® (Amgen)	Etanercept-szzs	August 30, 2016
Amjevita® (Amgen)	Humira® (AbbVie)	Adalimumab-atto	September 23, 2016

Pharmaceuticals and Medical Devices Agency (PMDA) approved biosimilars

Product name	Active substance	Company	Approval/ launch date
Epoetin alfa BS	epoetin alfa	JCR Pharmaceuticals	20-Jan-10
Filgrastim BS	filgrastim	Fuji Pharma Mochida Pharmaceutical	21-Nov-12
Filgrastim BS	filgrastim	Sandoz	24-Mar-14
Filgrastim BS	filgrastim	Teva Pharma Japan/Nippon Kayaku	28-Feb-13
Infliximab BS (Remsima)	infliximab	Celltrion/Nippon Kayaku	4-Jul-14
Insulin glargine BS	insulin glargine	Eli Lilly/Boehringer Ingelheim [2]	26-Dec-14
Insulin glargine BS	insulin glargine	Biocon/Fujifilm Pharma [3]	28-Mar-16
Nesp	darbepoetin alfa	Kyowa Hakko Kirin	13-Sep-13
Somatropin BS	somatropin	Sandoz	22-June-09

Exchange Rate of Dollar with various currencies:

All currencies converted assuming fixed exchange rate as on October 2016

1 USD = 66.5 INR

1 USD = 0.89 EURO

1 USD = 1102.45 WON

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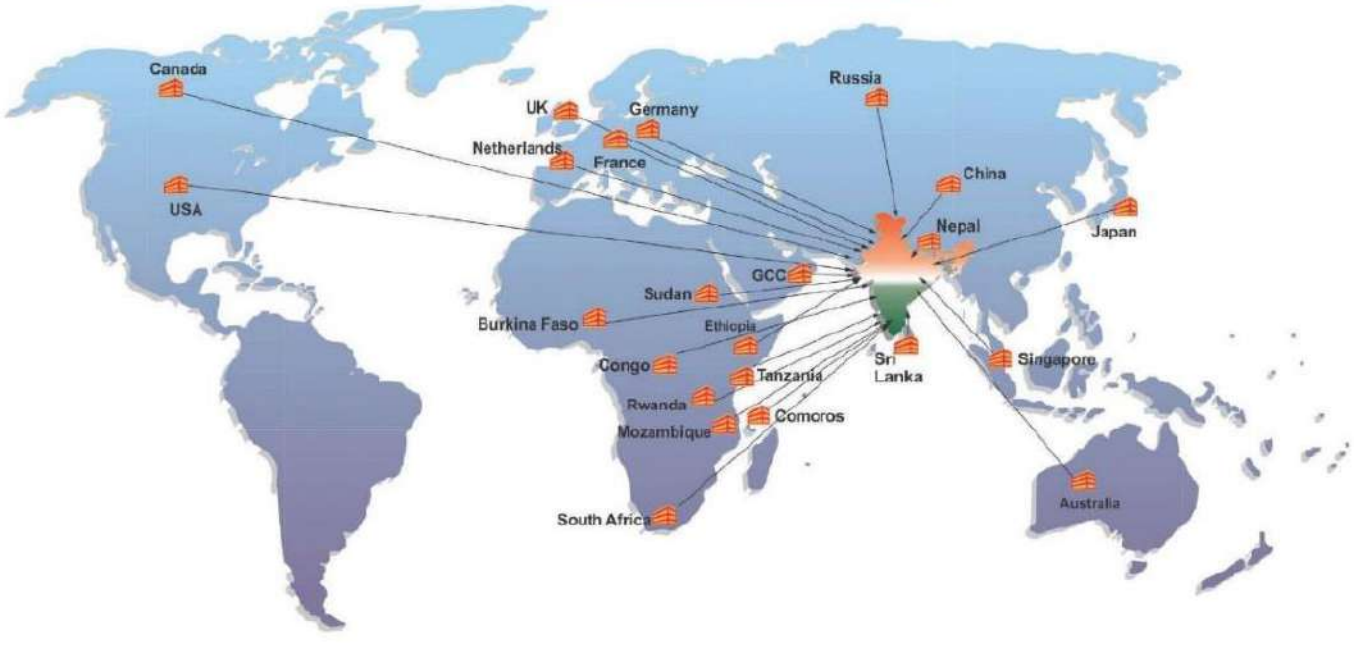

The pictorial presentation of the world map does not purport to be the political and geographical maps of the world and India and is not drawn to scale. This is only indicative.

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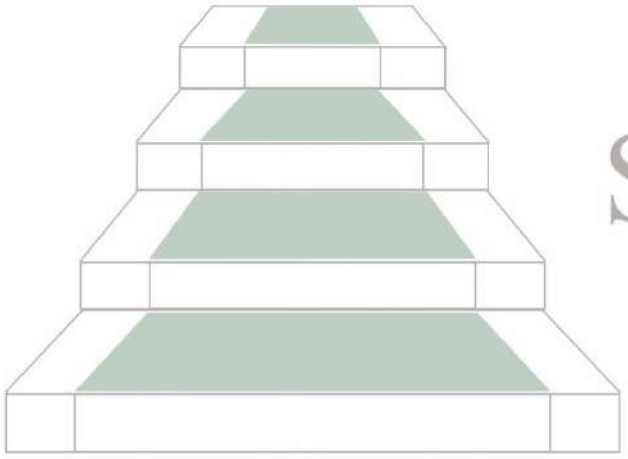

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