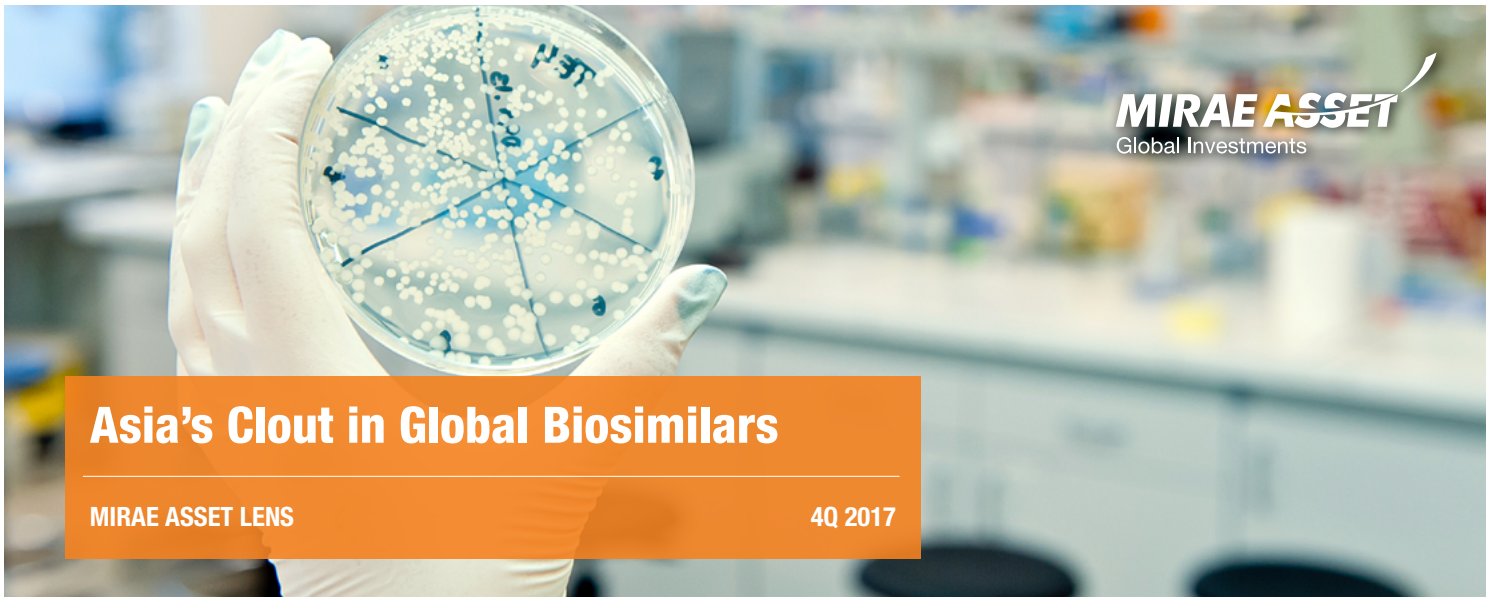

Asia's Clout in Global Biosimilars

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Sizing up the opportunity

The global biosimilar market is still in its very nascent stage. US$200bn in biotechnology drug brand sales is set to be genericized in the next decade.[1] This poses a meaningful opportunity for biosimilar companies, given that pricing discounts for biosimilars could be much lower than small molecule generics. Asian players are highly competitive and are vying for wallet share in developed markets.

Setting the Scene

Prior to assessing the landscape, it is important to better understand this new category of medicine. Biologic drugs (biologics) are derived from living organisms or contain components of living organisms. Biologic drugs are derived from human, animal, or microorganisms using biotechnology and include vaccines, blood, blood components, cells, allergens, genes, tissues, and recombinant proteins.

A biosimilar is a biologic medicine that is approved based on showing that it is highly similar to an existing approved innovative biological product, known as a reference product. However, unlike generic medicines, in which the active ingredients are identical to the reference small–molecule drugs, biosimilars will not be identical to the reference biologics due to several factors, including the inherent complexity of biologics and the proprietary details of the reference product. Below we compare the differences between these two types of pharmaceutical drugs.

Biosimilars vs Generics

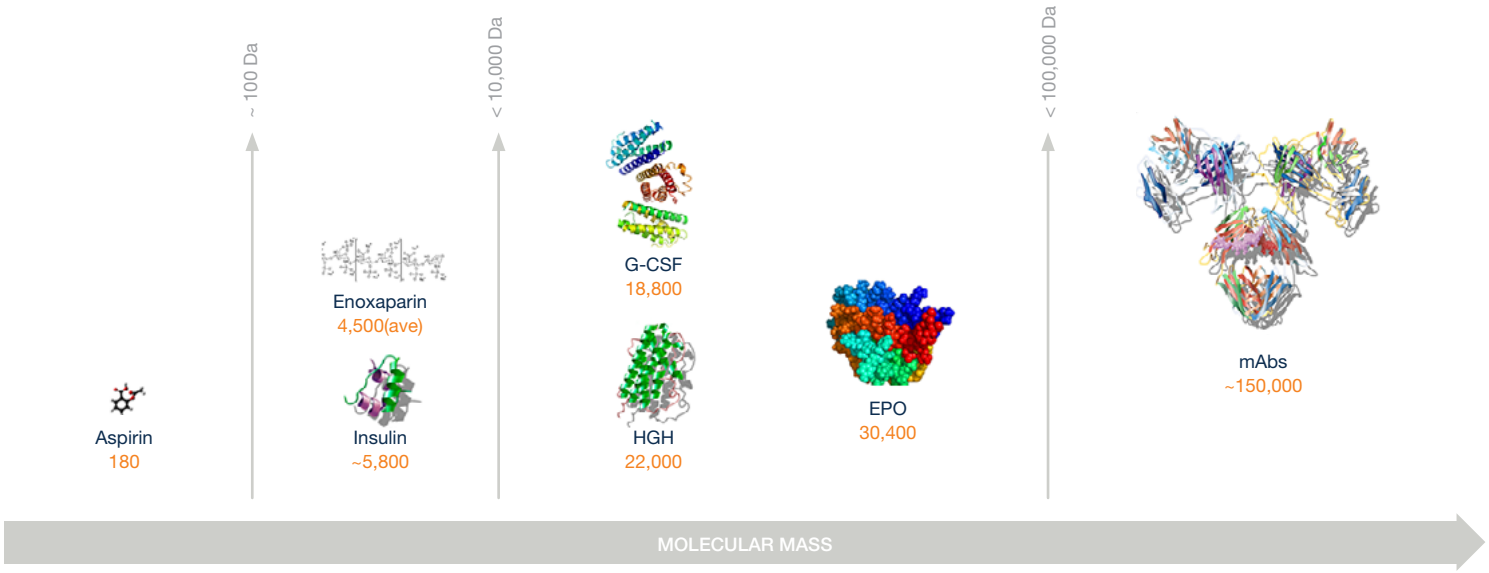
Source: Amgen (2017)

PROPERTIES	GENERICS	BIOSIMILARS
SIZE	Small	Large
MOLECULAR WEIGHT	~150 Daltons	~150,000 Daltons
STRUCTURE	Simple and well-defined	Complex with potential structural variations
MANUFACTURING	Predictable chemical process to make identical copy	Specialized biological process to make similar copy
COMPLEXITY	Easy to fully characterize	Difficult to characterize
STABILITY	Relatively stable	Sensitive to storage and handling conditions
ADVERSE IMMUNE REACTION	Lower potential	Higher potential
MANUFACTURING QUALITY TESTS	≤ 50	≥ 250
APPROVAL REQUIREMENTS	Small clinical trials in healthy volunteers	Large clinical trials in patients

[1] Morgan Stanley (2017)

Comparison of Molecular Mass of Small-Molecule (Chemical) Drugs Versus Large Biologics

Source: Amgen (2017)



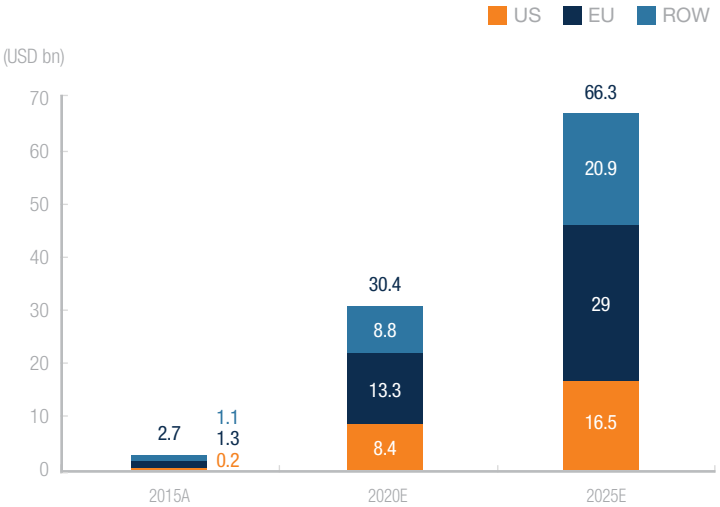
Ave=average; DA=Daltons; EPO=erythropoietin; G-CSF=granulocyte colony-stimulating factor; HGH=human growth hormone; mAbs=monoclonal antibodies.

Regulatory Diversity

The growth in biosimilars will be driven by biologics rolling off patent, first-time biosimilar approvals and market expansion from end-user uptake. These forces will occur across geographies, with the US and EU comprising the largest markets given that they are overseen by single regulators. While the first biosimilar was approved in 2006 in EU and in 2015 in US, the first complex biosimilar was approved as recently as June 2013 by the European Medicines Agency (EMA) and April 2016 by the US Food and Drug Administration (USFDA) in the form of mAbs. As regulatory precedents are established, we expect a bigger influx of biosimilar products going to market. Biologics accounted for seven of the ten best-selling drugs in 2016 globally, indicative of the commercialization potential.

Global Biosimilar Drug Market Forecast by Geographies (US$ billion)

Source: Frost & Sullivan (2017)



Europe is at the forefront of biosimilars adoption, and it created a supportive regulatory regime early on while the regulatory models remain underdeveloped in other regions. So far, Europe has introduced biosimilars of five reference products: Epogen, Neupogen, Remicade, Enbrel, and, most recently, Rituxan.

The first mAb Remicade captured approximately 50% market share within 30 months of post-initial approval. Enbrel biosimilar garnered 48% market share in UK and 29% in Germany within the first year of launch.[2] These market entry cases bode well for others in the future.

Best-selling drugs in 2016: Biologics Account for 7 of Top 10

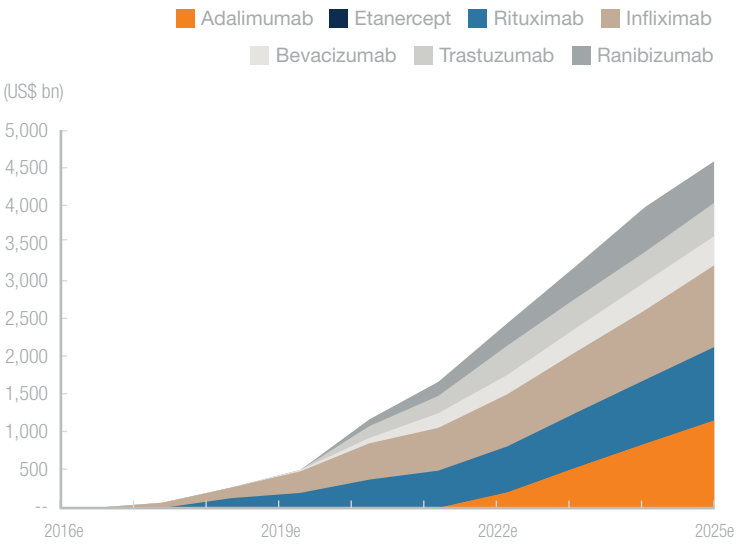
Source: EvaluatePharma, Samsung Securities (2017)

Rank	Product Name	Company	2016 Sales (USD bn)	2013-2016 sales CAGR (%)
1	Humira	AbbVie	16.5	14.7
2	Enbrel	Amgen/Pfizer	9.2	1.8
3	Harvoni	Gilead	9.1	106.6
4	Remicade	J&J/Merck	8.9	-3.0
5	Rituxan	Roche	7.4	0.4
6	Revlimid	Celgene	7.0	17.7
7	Avastin	Roche	6.9	0.7
8	Herceptin	Roche	6.9	1.6
9	Januvia/Janumet	Merck	6.4	3.3
10	Lantus	Sanofi	6.3	-5.9

We believe that the USFDA regulatory regime has been broadly conducive for biosimilar development. Products with no scientific issues were, rather sharply, pushed through admissions committee reviews and broad extrapolation was allowed. However, innovator companies are building defensive strategies around secondary patents, as seen in the likes of Humira and Enbrel, which could delay biosimilar launches. Nonetheless, the US market is forecasted to grow from a low base of US$0.2bn in 2015 to US$8.4bn in 2020, propelled by the immunology segment.[3]

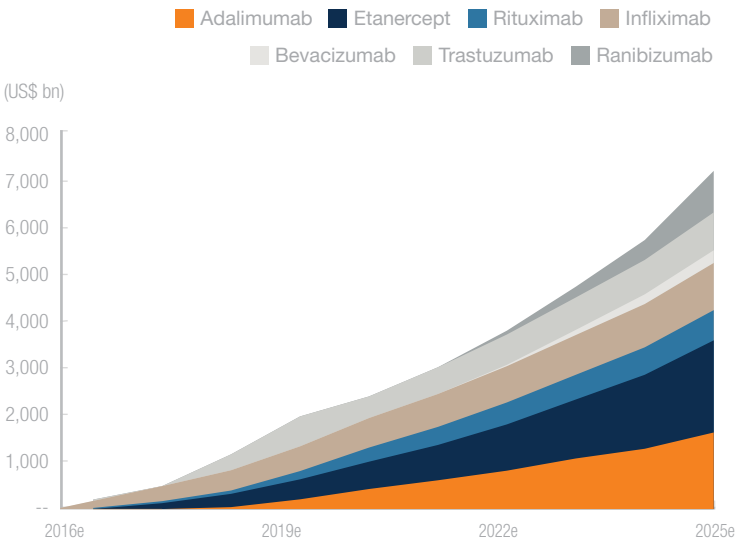
US Biosimilars Sales Opportunity of US$4.5bn by 2025e

Source: Morgan Stanley (2017)



EU/RoW biosimilar opportunity of US$7bn by 2025e

Source: Morgan Stanley (2017)



[2] Alliance Bernstein (2017)
[3] Frost & Sullivan (2017)

Interchangeability

Lack of interchangeability – producing an equivalent clinical result as a reference product in patients – will lead to a gradual ramp up for biosimilars. Interchangeability implies that distributors drive market share changes among manufacturers while lack of interchangeability would shift control to the physician level. While lack of interchangeability will lead to measured but stickier market shares for first-mover biosimilar companies, interchangeability implementation will benefit late stage entrants to gain market share with steeper discounts. USFDA's draft guidelines in early 2017 require a 'totality of evidence' approach to determine an interchangeable biologic. This is separate from biosimilarity and requires additional evidence, including detailed patient-switching studies.

Consistency is Key

Developing a biosimilar is a far more nuanced and complex process than developing a generic drug. Capital expenditures for this new class of drugs are considerable. A biosimilar will cost US$100mn to US$200mn in investment and eight to ten years of development time to bring to market. A small–molecule generic will cost US$1mn to US$5mn and take three to five years to develop.[4]

A biosimilar is typically subject to about 250 in-process quality tests during manufacturing, compared with about 50 tests for a small molecule generic. Biosimilars, like all biologics, are produced through an intricate, multi-step process, using living cells.[5]

Consistency is the key. Mass production involves a number of proprietary steps and conditions, including the method of cell line expansion, bioreactor conditions, protein extraction and purification, formulation and packaging. A change to any of these can affect the complex structure of the biosimilar, potentially altering one or more critical quality attributes (CQAs)

High Entry Barriers

We believe that the global biosimilar market will be lucrative in view of structural complexity relative to small molecules, a changing regulatory environment, and various demonstrable analytical capacities and clinical outcomes to gain regulatory approvals. The profit potential of the biosimilar market and progressively favorable regulatory approach has attracted the usual generic players as well as newcomers, and even innovative biotech companies. Altogether these firm-level and macro forces form significant barriers to entry. Companies need to demonstrate a highly coordinated set of capabilities for competitiveness, including:

- **Development and manufacturing capabilities:** Efficient manufacturing capacity with higher titer and purity, which in turn drive production yield. Optimal cell lines and cell culture conditions are critical.

- **Biosimilarity with originator biologic:** Robust analytical methods for physicochemical and functional analysis are needed to demonstrate biosimilarity. Non-clinical animal studies (toxicology, pharmacokinetic and pharmacodynamics studies and immunogenicity) are required to assess potential safety and activity in humans.

- **Clinical trial design:** Clinical trials generally account for the majority of development costs. Clinical trial design and conduct must satisfy the guidelines of more than one regulatory agency.

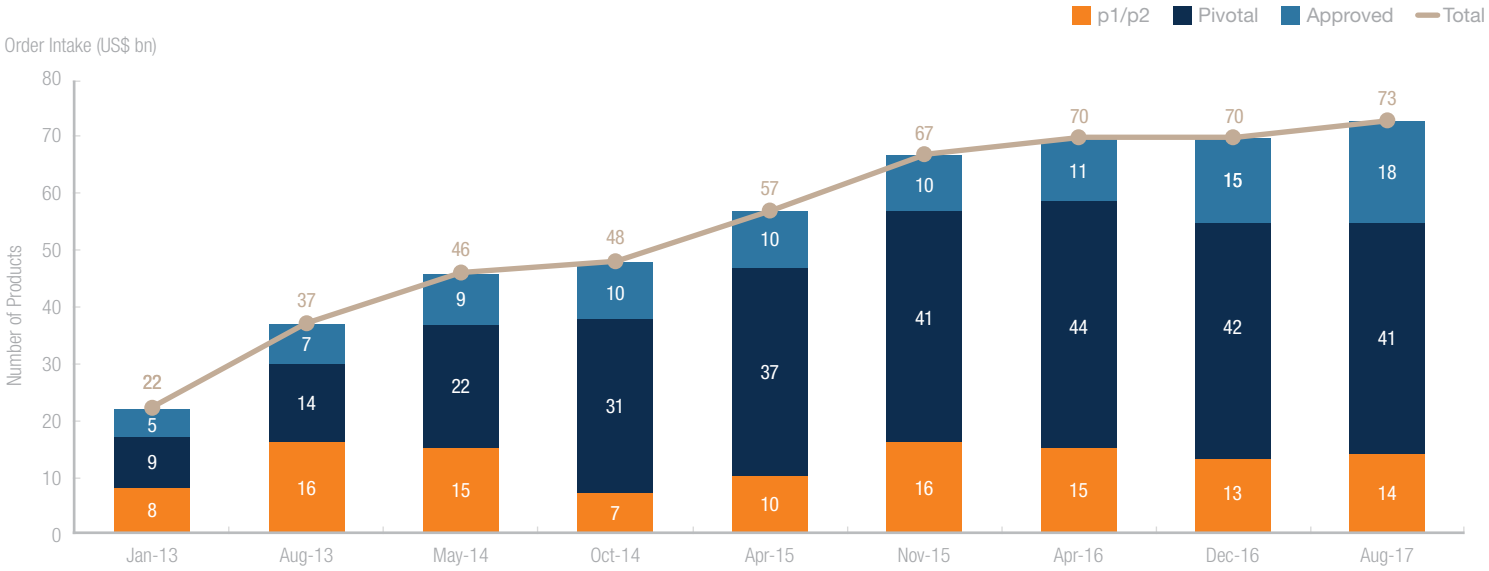
- **IP and Regulatory Compliance:** Understanding innovators patent landscape to ensure own products are approvable through design-around, non-infringement/patent invalidation would be critical toward commercialization of products.

- **Reliable commercial-scale supply capabilities**

[4] Mirae Asset Global Investments Research (2017)
[5] Mirae Asset Global Investments Research (2017)

Competitive Intensity Increasing Over Past Few Years: Progression of Clinical Biosimilar Pipeline

Source: Clinical Trial Registries; Company Disclosures; Bernstein Analysis (2017)



The Winning Formula

Companies leading the development cycle with strong research and development investment and immense manufacturing infrastructure will benefit from the upcoming biosimilar wave. We have identified several appealing players in the Asian region that are proving themselves on the global stage.

Asia Leads the Pack

Asian companies are leading the pack in seizing the global biosimilar opportunity. While the Celltrion Group has been in the forefront, other companies in the space including Samsung Bioepis, Biocon, and Dr Reddy's. Below is a snapshot of the top six biologics products and their competitive landscapes. In our assessment, we have considered companies that are either approved or have filed for regulatory approval in US/EU.

De-Risking Through Partnerships

Given the high initial cost of initial R&D, complex patent labyrynths, and the lack of interchangeability, most companies in Asia have chosen partnership models in order to de-risk their investments. The biosimilar companies focus on research and development, while partners focus on regulatory approval, litigation risks, and marketing activity. Most partners are global pharmaceutical companies with an established and strong presence in developed markets.

Product	Ingredient	Sales (US$ bn)	Indication	Filed / Approved	
				Asian Companies	Global Companies
Humira	Adalimumab	16.1	Inflammation	Samsung Bioepis	Amgen, Boehringer Ingelheim
Enbrel	Extanercept	8.6	Inflammation	Samsung Bioepis	Sandoz, Coherus, LGLS
Rituxan	Rituximab	7.3	Oncology	Celltrion, Samsung Bioepis	Sandoz
Remicade	Infliximab	6.9	Rheumatoid Arthritis	Celltrion, Samsung Bioepis	
Avastin	Bevacizumab	6.8	Oncology		Amgen
Herceptin	Trastuzumab	6.8	Oncology	Biocon, Samsung Bioepis, Celltrion	

Asian Biosimilar Players	Partnes
Celltrion	Pfizer / Teva
Samsung Bioepis	Merck / Biogen
Biocon	Mylan
Dr Redd's	Merck Serono

Celltrion Group

Celltrion Group is the leading biosimilar company in Asia. They developed the first biosimilar monoclonal antibody (infliximab) to be EMA approved for EU, which occurred in 2013. The firm entered biologics as a Contract Manufacturing Organization (CMO) in 2005 to commence global clinical trials for its first biosimilar candidate infliximab in 2010. It currently owns two monoclonal antibodies approved in EU and one in the US and has pipeline of seven biosimilars at various stages of development.

Celltrion Pipeline – Leading Position in Top 3 Products

Source: Company Disclosures, Morgan Stanley (2017)

Original Drug	Biosimilar Sponsors	Stage Of Development					Milestones
		Pre-Clinical	Phase 1	Phase 3	Filed	Approved	
Remicade INFLIXIMAB	**Celltrion**						
	Merck / Samsung Bioepis						
	Pfizer			Halted (2015)			
	Amgen						
	Sandoz						
Rituxan / MabThera	**Celltrion**						- by EMA
	Sandoz						- by EMA
	Pfizer						
	Amgen						
	Dr. Reddy's						
	Merck						
Herceptin trastuzumab	**Celltrion**						
	Amgen						
	Merck / Samsung Bioepis						
	Mylon / Biocon						
	Pfizer						
	Dr. Reddy's						

Samsung Bioepis

A late entrant into the biosimilar space, Samsung Bioepis owns a strong pipeline of six candidate drugs with one approved in the US and two in the EU. Samsung Bioepis is a joint venture established in 2012 between Samsung Biologics and Biogen Idec, combining Biogen's protein engineering and biologics manufacturing capabilities with Samsung's execution capability.

Samsung Bioepics – Gaining Scale

Source: Company Disclosures (2017)

Drug / Drug Candidate	Originator Biologic (Therapeutic Area)	Stage Of Development And Commercialization					Development Responsibility	Commercial Partner
		Phase 1	Phase 2	Filed	Approved	Launched		
SB4-Etanercept	Enbrel® (Immunologic)						SAMSUNG	MERCK Biogen
SB2-Infliximab	Remicade® (Immunologic)						SAMSUNG	MERCK Biogen
SB5-Adalimumab	Humira® (Immunologic)						SAMSUNG	MERCK Biogen
SB3-Trastuzumab	Herceptin® (Oncology)						SAMSUNG	MERCK
SB8-Bevacizumab	Avastin® (Oncology)						SAMSUNG	MERCK
SB9-Insulin Glargine	Lantus® (Metabolic)						MERCK	MERCK

Biocon

Biocon is one of India's champion biosimilar development companies. Biocon entered a partnership with Mylan in 2009. While Biocon will leverage its fermentation technology, Mylan will contribute its global commercial footprint and regulatory expertise. Biocon has four candidate medicines that are in late-stage development and is the first company to file for US approval for biosimilar Herceptin.

Biosimilar Bioepics: Bicon well placed in the competitive landscape

Source: Company Disclosures (2017)

Molecule	Biosimilar Development Pipeline@					
	Phase 1	Phade 3	Regulatory Submission		Approved / Marketed	
			EMA	FDA	EMA	FDA
Pegfilgrastim	Dr. Reddy's, Pfizer	Apotex, Cinfa, Sandoz	**Biocon**, Coherus	**Biocon**	None	None
Trastuzumab		Hanwha, Pfizer, Samsung	**Biocon**, Amgen, Pfizer, Celltrion, Samsung	**Biocon**(+ve ODAC), Amegen, Celltrion	None	None
Insulin Glargine			**Biocon**	**Biocon**	Eli Lilly, Merck	Eli Lilly, Merck(TA)
Adalimumab		Coherus, **Biocon**, Momenta, Pfizer, Fresnius, Sandoz, Fuji-Kirin, Oncobiologics)	BI, Fuji-Kirin, Sandoz	Samsung	Amgen, Samsung	Amgen, BI
Bevacizumab	Sandoz, Daiichi, Oncobiologics	BI, Pfizer, Samsung, Fuji-Kirin / Astra Zeneca, **Biocon**, Dr. Reddy's	Amgen	Amgen(+ve ODAC)	None	None
Filgrastim	Pfizer			Apotex	Sandoz, Teva, Pfizer, Stada, Apotex	Sandoz, Teva
Etanercept	Hanwha	Coherus, Lupin, Samsung			Samsung, Sandoz	Sandoz
Insulin Aspart						
Insulin Lispro					Sanofi	Sanofi(TA)
Rh-Insulin						

Asian Players in an Energetic Space

Biosimilars are a nascent drug technique and the industry hinges on regulatory approvals and capital-intensive development cycles. We are at the beginning of a megatrend of fusing biologics with medicine, and market size is predicted to expand considerably in the years ahead. We will be closely monitoring Asian players in the global marketplace as developments unfold. Investors should be doing the same as this healthcare segment is a theme too significant to ignore.

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