Global Biosimilars Outlook – 2019 & Beyond

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Executive summary (1/3)

- Biosimilars are emerging as one of the most important sectors in the healthcare industry to curb increasing healthcare costs, primarily associated with biologics
  - Biopharma has accounted for nearly one-half of the inflation in healthcare costs in the US, primarily due to the launch of innovative biologics
- Biosimilars will bring about much deeper market penetration among the patients across economic spectrum with rapidly declining costs, both in developed and emerging markets
  - Market size will multiply with increasing discounts
  - Margins will remain much more robust than the small molecule generics
- **With 15+ biologics losing patent by 2020, >70 pharma companies have >200 biosimilars in pipeline globally, to participate in $40B opportunity by 2025**
  - First wave biosimilars face growing competition, leaving few opportunities for newcomers
  - Next wave biosimilars too call for a solid foundation, giving first wave competitors a major edge
- Regulatory and payer landscape is evolving rapidly, with increasing support for biosimilars from multiple stakeholders
  - First mover multinational companies have invested heavily in select biosimilars portfolio
  - Originator companies have put up clever barriers for biosimilars competitors
  - Near term outlook is murky, but ultimate outcome is likely to mirror the evolution of small molecule generics landscape, only faster

Executive summary (2/3)

- Price competition is already intensifying, with 60+% discounts not uncommon
  - A clear regulatory path reducing development costs, volume scales for cost effective manufacturing, substitutability guidelines on the horizon, and payer groups favoring biosimilars — all add up to higher discounts
  - A handful of companies with a broad portfolio and global reach, combined with reliable and quality supply will capture a major share of the biosimilars market
- Development and market strategy will vary between the geographies
- **EU is matured market and biosimilars penetration in EU5 countries suggest that the market is gearing up for biosimilars competition**
  - Heterogeneous penetration due to differences in tendering/purchasing policies in each state
  - With intense competition foreseen, what will it take to sustain the biosimilars growth?
    - Better prescribers incentives, positive switching policies and multiple winning tenders will ensure broader uptake in the future
- **How long will it take for the US to deliver on the potential biosimilars market in its own way?**
  - Rise in number of approvals and increasing the biosimilars penetration, although modest, are early signs of the potential growth in the coming years
  - High competitive intensity is expected as the regulatory guidelines are favoring biosimilars and substitutability will soon becomes a norm

Executive summary (3/3)

- Payer groups are increasingly taking initiatives to give preference to biosimilars, almost akin to substitution

- **Japan is a unique yet a lucrative market for biosimilars in the coming years**
  - Japan's biosimilar market is set for accelerated growth with several active government programs promoting biosimilars and several major biologics losing patents
  - "Biosame" entry, uninterrupted supply and companies' strong front-end footprint are the key determinants of success
  - Many international and domestic drug developers have joined the biosimilar foray with partnerships with local companies having a front-end capabilities
  - Japan has witnessed mixed performances of existing biosimilars, mainly attributed to product wise difference in the co-pay system, use in DPC hospitals and companies' strong front-end skills
  - "Biosame" era – A roadblock for mid-sized Japanese biosimilars developers or limited to few products only?

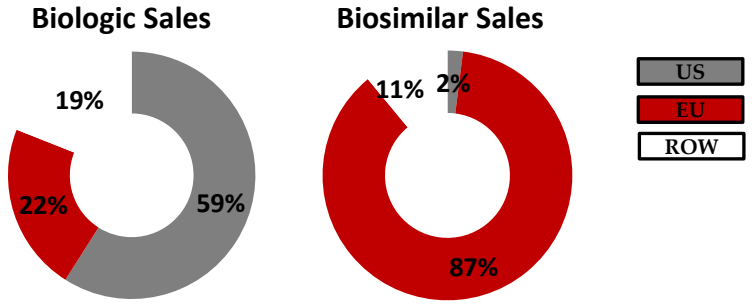
- **Early acceptance of biosimilars in emerging markets like India and China is enabling a select group of biosimilar companies to achieve market position and cash-flow positive operations**
  - While the Chinese and Indian companies have developed several complementarities required for global leadership, collaboration between the two has the potential to attain global leadership in biosimilars space, determining the real success
  - While Indian companies bring broader portfolio, western regulatory experience and marketing front end and emerging market experience, China has the access to capital, technical skill sets and marketing experience for China market

1. Global Biosimilars Landscape Overview

- Evolving Biosimilars Opportunity
  - A $40B opportunity worldwide by 2025
- Biosimilars Market Landscape
  - EU and Emerging markets strong, while uptake in the US and Japan gaining momentum
  - Fluid regulatory, political and market landscape offers an opportunity to gain leadership with broad portfolio initiatives
- Regulatory Landscape
  - EU, Japan and Emerging countries set the pace, while the US is shaping up
- Growing Competition Across the Geographies
  - Globally, over 200 biosimilars for more than 50 biologics are being developed by about 70 companies
  - With first wave biosimilars facing high competition, next wave biosimilars are the key focus

Biosimilars sales & market size

- Biologics sales WW are over $250B
  - ~2% ($5B) of the overall biologics sales were contributed by biosimilars in 2017, which is likely to triple by 2020
  - At least $200B of biologics sales face biosimilars competition, which should amount to at least $40B in biosimilars sales in the near future—even at a 80% discount to the originator's price
- Europe accounts for 87% of global biosimilars sales of $5B, compared to just 2% from the US, even as the US accounts for 59% of branded biologic sales vs only 22% coming from Europe
- Globally, over 200 biosimilars for more than 50 biologics are being developed by about 70 companies in various phases of development
- As many biopharma companies developing biosimilars focus on developed markets, accelerating competition promises to bring prices down considerably
- Over the coming decade, massive unmet demand in emerging markets also promises to offer an attractive opportunity



Source: Company Reports, MP Analysis

Biosimilars – evolving regulatory pathway

Parameters	Innovator Brands	Biosimilars Today	Substitutable Biosimilar Generic Tomorrow
Clinical Development	Extensive clinical studies- PK/PD and phase I, II and III	At least one clinical study - PK/PD and phase I and III; some cases only phase I	Often only Phase I, after rigorous PK/PD
Indications - Extrapolation	Clinical data required for all indications - extrapolation not allowed	Clinical data required for only one representative indication - extrapolation case by case	Often only Phase I, after rigorous PK/PD, referencing innovator data
Maturing Regulation to Substitutability	-	Demonstrate similarity – no automatic substitution in most developed regions	Demonstrate equivalence - substitution with maturing regulations may be allowed
Manufacturing Evolution	Multiple site changes, including CMOs, watched by innovator deemed identical	Biological process difficult, but equivalence definition per maturing regulations	Mature regulations to yield a clear path to equivalent finished product protocols
Cost of Development	$1B	$100-200m	$10-20m
Time to Development	10+ years	5+ years	2+ years
Potential for Exclusivity	Up to 12 years	Up to 1 year possible	Up to 1 year possible
Discounts to Originator Price	-	30+%	Up to 80%

The future biosimilars will be more like today's generics where they require baseline clinical studies, lowering the development cost and faster approvals that will continue to accelerate competition leading to lower prices

Source: Company Reports, MP Analysis

Biosimilars uptake – current and future

Region		Regulatory Guidelines Evolution		Access to Biologics		Payer Assessment & Access		Prescriber Acceptance		Patient Acceptance		Biosimilars Presence	
	Initial Guidelines	2019	2021	2019	2021	2019	2021	2019	2021	2019	2021	2019	2021
EU	2000	◕	●	◕	◕	◕	◕	◑	◕	◑	◕	54	70+
US	2009	◑	◕	◕	◕	◔	◑	◔	◑	◔	◑	26	35+
Japan	2009	◑	◕	◕	◕	◑	◕	◔	◑	◔	◑	25	30+
China	2015	◔	◑	◔	◔	◔	◑	◔	◑	◔	◑	1	10+
India	2012	◑	◑	◔	◔	◔	◑	◔	◑	◔	◑	65	70+

- Across European countries, differences exist in biosimilars policies leading to variations in its uptake and divergences in savings from biosimilars use; most countries have established specific supply-side policies for promoting access to biosimilars
- A balanced regulatory framework is evolving in the US, with inclusion of substitutability, along initiatives to increase the update by payers in-parallel
- Strong government promotional measures to use biosimilars, at least in DPC (Diagnostic Procedure Combination payment system) hospitals, will further drive penetration in Japan
- Biosimilars uptake in developing markets such as China and India are largely dependent on patient spending power, given the large proportion of out-of-pocket healthcare spend in these countries

Status/Prospect ◔ Low ◑ Medium ◕ High

Source: Company Reports, MP Analysis

Country wise biosimilars development

Country/Region

EU		US		Japan		China		India	
Mabion SA	7	Mylan	11	Gene Techno Science	4	Shanghai CP Guojian	9	Reliance Life Sciences	20
Alvotech	6	Pfenex	7	Daiichi Sankyo	3	Zhejiang Huahai	8	Zydus Cadila	11
Pol Pharma	5	Momenta	6	Meiji Seika Pharma	2	3SBio Inc	7	Dr. Reddy's	11
Stada Arzneimittel Ag	3	Coherus	5	Fuji Pharma	2	AlphaMab	7	Biocon	7
Gedeon Richter	3	Merck Sharp & Dohme	5	Mochida	1	Shanghai Henlius Biotech	7	Cipla	6
Stada Arzneimittel Ag	3	Amgen	4	Kissei	1	Bio-Thera Solutions	5	Lupin	5
Xbrane	3	Pfizer	4	Kyowa Hakko Kirin	1	Zhejiang Hisun	5	USV	5
Formycon	3	Samsung Bioepis	3	Nippon Kayaku		Luye Pharma Group Ltd	4	Intas	2
Fresenius	2	Apobiologix/Apotex	2	Nichi-iko		Jiangsu T-mab	3	Glenmark	1
Accord Healthcare	1	Adello Biologics	2	JCR		Qilu Pharmaceutical	3	Hetero drugs	1
Hexal Ag	*	Eli Lily	1	UMN Pharma		Walvax Biotechnology	3	Emcure	*
Nanolek	*	Boehringer Ingelheim	1	Aska Pharma		Innovent Biologics Inc	2	Genex Pharma	*
Sandoz GmbH	*	Outlook Therapeutics	1	Towa		Xiamen Amoytop	1	Panacea biotech	*
Medice Arzneimittel	*	Teva	*	Toyobo		Jiangsu Hengrui	1	Camus Pharma	*
Ratiopharma GmbH	*			Nipro Pharma		Changchun ChangSheng Gene	*		
Samsung Bioepis	*			Sawai					
Tech Dow Europe	*			Mitsubishi Tanabe					
Pharmathen SA	*			Fujifilm Pharma					
Cinfa Biotech	*			Yoshindo					
Egis	*								
Total	**31**	**Total**	**51**	**Total**	**14**	**Total**	**76**	**Total**	**69**

Note: -The number on the right indicates the number of biosimilars in development pipeline for each company based on publicly available information as of February, 2019
-* Indicates that the pipeline is undisclosed

Source: MP Analysis

Key biosimilars partnerships (2017-2019)

Deal Date	Recipient-Acquirer	Deal Geography	Deal Value ($m)
2/28/2018	Revance - Mylan for development and commercialization of botox biosimilar	Asia-Pacific, Europe, Middle East and Africa, North America, South and Central America	355.00
11/6/2019	Samsung Bioepis -Biogen for ranibizumab and aflibercept	Australia, Canada, China, Europe, Japan, United States	310.00
5/7/2018	mAbxience - Amneal for bevacizumab	United States	71.80 *
8/4/2017	Shandong Bo'an Biotechnology - Luye Pharma for denosumab	China	66.90
11/4/2019	Alvotech -Yas Holding for commercialization of three biosimilars	Middle East and Africa	45.00
6/11/2018	Pfenex - Alvogen for commercialization of teriparatide	United States	27.50 *
4/18/2018	Pfenex - China NT Pharma for development and commercialization of teriparatide	China, Hong Kong, Malaysia, Singapore, Thailand	25.00 *
6/28/2018	Lupin - Mylan for commercialization of Enbrel	Asia-Pacific, Australia, Europe, Middle East and Africa, New Zealand, South and Central America	15.00 *
7/25/2017	Outlook therapeutics - GMS Tenshi for ONS-3010 and ONS-1045	Asia-Pacific, Middle East and Africa, South and Central America	10.00 *
7/12/2018	Xbrane - STADA for Xlucane	Asia-Pacific, Europe, Middle East and Africa, United States	8.80 *

- In the past two years, about 70 partnerships have taken place in the biosimilars market globally
- Partnerships/Collaborations have been the key driver for a company's success in biosimilars space

Note: * Deal includes a royalty/profit sharing component that is undisclosed

Source: Company Reports, MP Analysis

The way forward

- With an opportunity of at least $40B in biosimilars sales in the near future, and $100B within the decade, this high margin biosimilars growth opportunity can also help accelerate global reach
- In such a dynamic landscape, no single biosimilar company has been able to thrive without collaborating in some way or the other
  - Where time is of the essence, rapidly trading- off resources based on dynamic market conditions and partnering to capture opportunities is the way forward
  - A more attractive approach may be to find a strategic partner, particularly when one partner has expertise in contracting/tendering and access to key channels, and the other brings development + manufacturing strength
  - Presence in emerging markets would be of equal importance, if not more, than developed markets, when it comes to scale and revenues to build cost-effective market access to fully leverage initial large investments
- New entrants can prove their prudence of not being among the first with bold yet prudent collaboration with one of the short list of established biosimilars companies, helping accelerate combined portfolio and geographic reach to become one of the six companies likely to dominate
  - The new entrants in biosimilars space have already missed the bus for the first wave of biosimilars and therefore, should focus on the next wave of products
  - For wave 2 and 3 biosimilars, right selection of products, therapy area and region will be instrumental in achieving long term success—ideally with a partner so as to not to reinvent the wheel
  - It is the right time to enter the biosimilars space with the next wave of products as clarity in regulatory guidelines and increasing adoption for biosimilars globally continue to make this a timely opportunity

3. EU Biosimilars Landscape

- With EU being the most matured market shows varying penetration between the member states

- Competitive Landscape
  - Highest number of biosimilars approvals contributing >80% of the worldwide biosimilars sales
  - >30 biosimilars, primarily mAbs in late phase development

- EU5 Biosimilars Adoption
  - Switching polices, prescriber incentives, pricing and tendering activity are the key factors impacting the biosimilars adoption
  - Market access, biosimilars procurement process and pricing policies differ between member states causing variability in the uptake

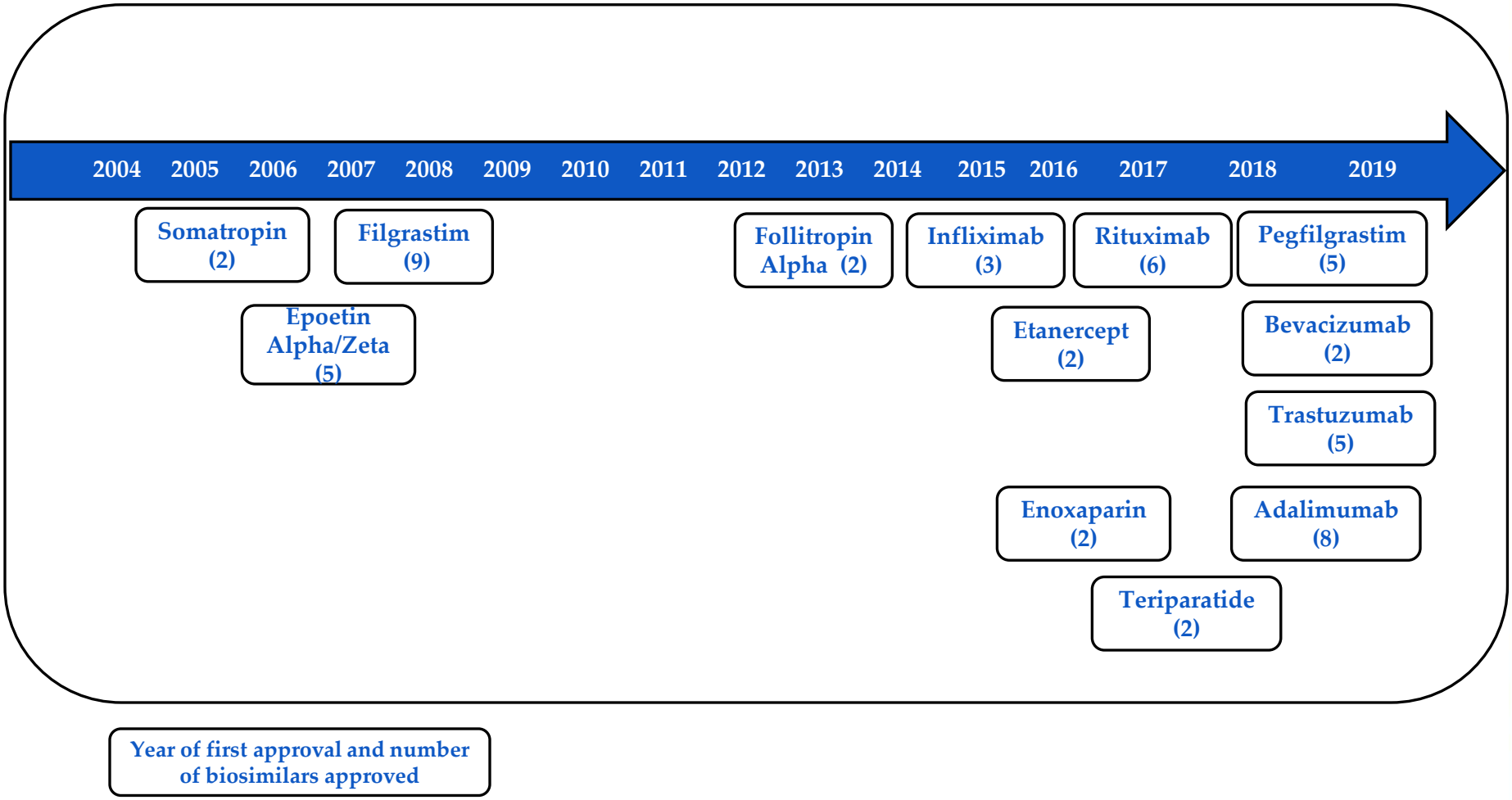
- Factors Impacting Market Sustainability of Biosimilars in the EU
  - Prescriber incentives and tendering methods will have the major impact on the continuous expansion of biosimilars penetration

EU biosimilars landscape

- EU contributed to ~85% of the global biosimilars sales with ~ $3B in 2018
  - Presently, 54 biosimilars have been approved for 15 originator products
  - ~15 companies focus biosimilars with Sandoz, Pfizer, Celltrion and Samsung Bioepis leading the race
  - Biosimilars will influence the healthcare savings of ~$8B between 2016-20 in EU5 countries (France, Germany, Italy, Spain, UK) alone
- While EMA regulatory guidelines favor biosimilars and are followed by all the member states, policy and marketplace differences at country level has resulted in variability in the uptake
  - Main factors contributing to higher adoption are prescriber incentives and tendering/contracting systems
  - Biosimilars discounts range from 10-90% depending on the product, competition and availability of reference products in the country of launch
  - Interchangeability is excluded from the EMA policy and is practiced at individual country level
  - Switching is mainly controlled by the physicians and automatic substitution largely doesn't prevail
- Life cycle management of innovator product, product demand, tender types and patient/physician incentives are some of the uptake barriers experienced in the EU
  - Epoetin, human growth hormones, fertility and insulin have faced slower uptake due to lack of awareness wheras recently approved biosimilars in anti-TNF and oncology space have witness higher and faster uptake
- While the EU market is now established for a decade, what will it take to grow and sustain in the future?
  - Prescriber incentives like gain sharing and prescriber quotas are likely to further increase the uptake
  - Multiple winner tendering process to ensure healthy competition and continuous investment in the biosimilars space

Source: Company Reports, MP Analysis

Approved biosimilars in EU for 15 biologics



Source: Company Reports, MP Analysis

Marketed biosimilars in EU

Products	EU Companies	International Companies	Marketed Biosimilars
Somatropin		Sandoz	1
Enoxaparin sodium	Pharmathen, Techdow		2
Teriparatide	Gedeon Richter, Stada		2
Epoetin Alpha	Stada =2*, Hexal AG, Medice	Pfizer, Sandoz	5
Filgrastim	Hexal, Ratiopharm	Accord, Apotex, Pfizer, Sandoz, Teva, Mylan	8
Folllitropin Alpha	Gedeon Richter	Teva	3
Infliximab		Pfizer, Sandoz, Celltrion, Samsung Bioepis	4
Etanercept		Sandoz, Samsung Bioepis	2
Rituximab		Celltrion=4*, Sandoz=2*	6
Pegfilgrastim	Mundipharma, Novartis AG	Mylan, Accord, Sandoz, Coherus	6
Bevacizumab		Amgen, Pfizer	2
Trastuzumab		Amgen, Pfizer, Samsung Bioepis, Mylan, Celltrion	5
Adalimumab	Fresenius	Amgen=2*, Samsung Bioepis, Mylan, Sandoz=3*	8

*Companies with several MAs for the same product approval for strategic reasons

Source: Company Reports, MP Analysis

Biosimilars competitive landscape – phase III/pending approval

Products	Companies	Biosimilars in Phase III	Biosimilars in PA
Filgrastim	Merck	1	-
Pegfilgrastim	Fresenius, Pfizer, USV	1	2
Etanercept	Coherus, Pfizer, Mylan	1	2
Infliximab	Amgen, Novartic AG	-	2
Trastuzumab	Eirgenix, Prestige, Henlius	1	2
Eculizumab	Amgen	1	-
Ranibizumab	Pol Pharma, Xbrane, Bioeq GmbH	3	-
Rituximab	Archigen, Amgen, Samsung Bioepis, Mabion, Pfizer	4	1
Adalimumab	Fresenius, Alvotech Mylan, Celltrion, Momenta	5	-
Bevacizumab	mAbxience, Centus, AstraZeneca, Fujifilm, Boehringer Ingelheim , Samsung Bioepis	6	1

Source: Company Reports, MP Analysis

Biosimilars adoption in EU5 countries

Countries	Switching/ Substitutability	Prescriber Incentives	Discounts to Reference Products*	Pricing	Biosimilars Procurement Method	Type of Tendering	Tender Activity
UK	Yes/no	Yes	30-90%	Free pricing	Tender	Hospital	Low
Germany	Yes/substitution mandated if same manufacturing source	Yes	30-70%	Free pricing	Direct negotiations	Hospital and Retail	High
France	Yes/Yes for new cases only	Yes	10-55%	Company + National authority	Tenders	Hospital	Medium
Italy	Yes/no	Yes	40-50%	Company + National authority	Tenders	Hospital and Retail	Medium
Spain	Yes/no	Yes	25-30%	Company + National authority	Tenders and direct negotiation	Hospital and Retail	High

- Tendering is a biosimilars procurement method at national, regional and hospital level where there is either a single winner or there are multiple winners
  - In single winner tendering a single company is awarded the full market
  - In multiple winner tendering, the strategy is such that no company is awarded the full market but each company would have an incentive to offer the most competitive price
- There are several prescriber incentives out of which the most popular are gain sharing and prescriber quota
  - Gain sharing is to push cheaper drug prescription where the savings are split between the payer and the prescriber/hospital
  - Prescriber quota are put in place by physician associations for target agreement on biosimilars prescription shares

*Discounts mostly keeping in mind Anti-TNFS

Source: Company Reports, MP Analysis, IQVIA Report 2019

United Kingdom

(Highest biosimilars penetration amongst EU5 countries)

Parameters	Current Status	Comments
Access	High	• All biosimilars available through hospital setting
Pricing	Free	• Free pricing by the company but regulated by tendering • Pharmaceutical price regulation scheme (PPRS) negotiations have volume based pricing scheme where government gets a rebate if the medicines are sold above the threshold
Discounts	30-80%	• Discounts vary from 30% to 80% depending on the number of competitors , therapeutic area, etc. • No mandatory discounts enforced by the government
Prescriber policies	Yes	• Financial incentives through gain sharing between budgets groups and prescribers • Education and trainings are being conducted to educate the prescribers
Switching	Yes	• Driven by prescribers only
Substitutability	No	• Pharmacy level substitution is not allowed; no such guidelines published by MHRA
Tendering	Yes	• Tendering is regional and primarily applied at hospitals • No separate tenders for naïve and patients already in treatment • Typical duration of a tender contract is 24 months • Single winner system in four regions now shifting to multiple winners across 11 regions for e.g. adalimumab tender was awarded to multiple winners in 11 regions
Uptake	Refer to the table below	• UK has the highest biosimilars uptake amongst the EU5 countries • Gain sharing policy is one of the main reasons for high uptake • NHS aims to cover 90% new patients with the lowest price biologics/biosimilars within 3 months of biosimilars launch and at least 80% of existing patients within 12 months

Somatropin	Epoetin alpha	Etanercept	Filgrastim	Follitropin alpha	Infliximab	Rituximab	Trastuzumab	Adalimumab
10%	10%	70%	100%	55%	90%	80%	60%	15% @ 4 months

Source: Company Reports, MP Analysis

Germany

(Country with maximum tender activity among EU5 countries)

Bioismilar Parameters	Current Status	Comments
Access	High	• All the biosimilars are available across hospital, retail and other settings
Pricing	Free	• Set freely by the company and negotiated through tenders • Biosimilars are included in the internal reference pricing system for reimbursement
Discounts	30-70%	• Discounts are not mandatory
Prescriber policies	Yes	• Prescriber incentives are as per the target agreement – prescriber quotas • Measures are being taken for continuous prescriber training and education
Switching	Yes	• Prescriber drives the switching
Substitutability	If manufacturing source is same	• Substitution allowed for biosimilars made by the same manufacturer eg, Remsima and Inflectra • Epoetin alpha, Filgrastim and Infliximab are automatically substituted due to sufficient market experience • Automatic substitution framework is being deliberated and likely to roll out by 2022
Tendering	Yes	• National and regional tendering applied to hospital as well as retail setting • The tender contracting time is 24 months • No separate tenders for naïve or in treatment patients • Tendering process highly fragmented that involves more than one winner
Uptake	Refer to the table below	• After UK, Germany has high uptake of biosimilars among EU5 countries • Germany has all the four Adalimumab biosimilars in the market

Somatropin	Epoetin alpha	Etanercept	Filgrastim	Follitropin alpha	Infliximab	Rituximab	Trastuzumab	Adalimumab
15%	84%	50%	85%	45%	50%	50%	25%	25% @ 4 months

Source: Company Reports, MP Analysis,

France

(Only country that allows molecule naïve patient substitution)

Bioismilar Parameters	Current Status	Comments
Access	High	• All biosimilars available through hospital setting except etanercept which is also available in retail
Pricing	Company + National authority	• No internal reference pricing system • Prices negotiated with the Economic Committee for Medicinal Products (CEPS) factoring volume forecasts, price of the originator in France and other EU countries, etc.
Discounts	10-55%	• Discount s 25-35% to the originator price; higher discounts typically in a retail setting
Prescriber policies	Yes	• Direct financial incentives in place
Switching	Yes	• Switching only allowed in naïve patients
Substitutability	Yes	• Legal framework in place for substitution for naïve patients • Automatic substitution not allowed
Tendering	Yes	• Primarily in hospital setting • Mostly single winner tenders • The duration of contract varies between the hospitals • Separate tenders for naïve and in treatment patients which is now being consolidated
Uptake	Refer to the table below	• Regional Health Agencies policy for biosimilars uptake encourages the hospitals to switch to biosimilars as soon as they are available • The aim of this is to have 70% patients on biologics to be on biosimilars as soon as possible • Not much incentives provided in retail setting and hence the uptake through retail is low

Somatropin	Epoetin alpha	Etanercept	Filgrastim	Follitropin alpha	Infliximab	Rituximab	Trastuzumab	Adalimumab
16%	35%	15%	95%	45%	55%	47%	28%	1%@ 4 months

Source: Company Reports, MP Analysis, IQVIA Report 2019

Italy

(Biosimilars are treated like generics, price cuts are mandatory with minimum 20% discount)

Bioismilar Parameters	Current Status	Comments
Access	High	• Biosimilars are available mainly in hospital and few in retail settings
Pricing	Company + National authority	• Price cuts are mandatory with minimum 20% discount
Discounts	40-50%	• The discount percent depends on the average public expenditure of originator in the last three years
Prescriber policies	Yes	• Biosimilars quota policies are in implemented but still the quotas have not been met in many regions
Switching	Yes	• Physician prefer originators over biosimilars
Substitutability	No	• Automatic substitution is not allowed
Tendering	Yes	• National, regional and local tendering • Tender contract time is 24 months • If there are more than 3 competitors of the same product, multiple winner tender is applied • No separate tenders for naïve and existing patients
Uptake	Refer to the table below	• On availability of the approved biosimilars authorities have to incorporate the use of those biosimilars within 60 days of launch • Physician prefer originators and hence the adoption is slow • Uptake is low as there are not many incentives for expensive treatments

Somatropin	Epoetin alpha	Etanercept	Filgrastim	Follitropin alpha	Infliximab	Rituximab	Trastuzumab	Adalimumab
15%	70%	35%	95%	38%	75%	45%	10%	10% @ 4 months

Source: Company Reports, MP Analysis, IQVIA Report 2019

Spain

(Biosimilars are considered hospital-only medicines)

Bioismilar Parameters	Current Status	Comments
Access	High	• All biosimilars available in only hospital setting
Pricing	Company + National authority	• The price of the biosimilars are negotiated
Discounts	25-30%	• List price cuts are of ~30%, additionally followed by large discounts on net price level
Prescriber policies	Yes	• Hospital pharmacists influence physicians to prescribe the respective biosimilar, offering the lowest discounts via tender/direct negotiations • No biosimilar quotas in place
Switching	Yes	• Physician prefer originator and hence the adoption is slow • Patient consent is required for switching
Substitutability	No	• Not much difference in the price between the originator and biosimilar drug hence switching not encouraged and automatic substitution not required
Tendering	Yes	• National, Regional and Hospital based tenders • Regional tenders offer multiple business opportunities for manufacturers
Uptake	Refer to the table below	• Currently, the overall uptake is low as compared to UK and Germany • Availability of lower treatment cost with biosimilars will increase the uptake in the future

Somatropin	Epoetin alpha	Etanercept	Filgrastim	Follitropin alpha	Infliximab	Rituximab	Trastuzumab	Adalimumab
5%	70%	25%	95%	50%	50%	10%	10%	1% @ 4 months

Source: Company Reports, MP Analysis, IQVIA Report 2019

Key factors ensuring broader uptake and sustainable biosimilars adoption

Parameters	Current Trends	Future Trends
Substitution	• Majority of the EU countries do not allow automatic substitution	• Substitution in all the countries for existing patients will be important for the uptake is likely to roll out the coming years
Prescriber policies	• Lack of confidence in prescribers with only a few countries having effective prescriber incentive policies in place	• Better prescriber incentives like gain sharing/prescriber quota and education will drive the future biosimilars uptake
Pricing	• Pricing policies vary between countries where only UK and Germany follow free pricing while in other countries biosimilars discounts are mandatory	• Free pricing policy in all member states will ensure healthy competition between biosimilars and innovators
Discounts	• Discounts range from 10-90% , mAbs are mainly discounted between 30-40% with some exceptions	• Discounts will be ~90% for mAbs, but unlikely to impact the uptake due to tendering process
Competition	• Competition is picking up with at least two players in the EU5 countries for approved biosimilars	• Intense competition is expected in the future mostly with mAbs, ensuring fair gains to all competitors in the market
Tendering	• Single winner leading to, lower penetration, early shortage of drugs and discouraging competition	• Multiple winners will lead to broader penetration, address the supply of drugs shortages and encourage more players and healthy competition

Current policy framework supports sustainability but further prescribers incentives, positive switching policies and multiple winning tenders will ensure broader uptake in the future

Source: Company Reports, MP Analysis

4. Biosimilars Landscape in the US –A Multi-billion Dollar Industry in Making

- Although EU adopted biosimilars a decade earlier, US is picking up
  - As compared to EU only half of the biosimilars have been approved in US as of today
- Current Biosimilars Challenges
  - Manufacturing complexities to legal, policy and regulatory barriers impact the biosimilars uptake
- US Biosimilars Landscape Today, Outlook Tomorrow
- Competitive Landscape Overview Early & Next Wave Biosimilars
  - An opportunity to gain leadership amidst the fluid regulatory and policy landscape

Evolution of biosimilars landscape to date

- Only 15 first wave of biologics losing patent vs 150 generics a generation ago
  - US took the lead with small molecule generics, but now playing catch-up
- Because of complexity, regulators are not ready with the framework
  - This in turn has given an opportunity to the originators to add additional barriers from patent walls to supplying their product
- Therefore, only 11 biosimilars have been launched leading to very modest discounting to date
- The question is when, not if, substitution with biosimilars will be a norm
  - Currently more than 25 biosimilars have been approved in the US compared to a few in 2017
  - Recent interchangeability guidelines is a positive step favoring biosimilars
- Next wave of biologic patent expiry to experience a normalized landscape
  - Patents for some of the reformulated first wave biologics also expiring then
- Innovator biopharma profits face strong headwinds from biosimilars
  - Over 80% discounting on $500B of most profitable innovator biologics sales could decimate margins in next decade

Source: Company Reports, MP Analysis

Current challenges for biosimilars uptake in the US

Regulatory Barriers

- Fluid regulatory landscape leading to high cost and long development timelines
- Unclear substitutability guidelines
- Sourcing of reference products

Legal Barriers

- Patent litigation by originator companies
- Delayed market entry and added cost of development

Manufacturing Complexities

- Reproducibility issues
- Low yield of the product, requiring large manufacturing capacities
- Switch from stainless steel bioreactors to single use bioreactors

Physician Acceptance

- Lack of confidence in switching to biosimilars
- Minimal price difference between bisoimilars and reference drugs
- No health policies that mandate the biosimilar use

Market Place

- Long term contracts of PBMs with originator companies
- Originators slashing down the prices to prevent biosimilars entry
- Originators launching new or alternative strength formulations

Source: Primary research, MP Analysis

US biosimilars landscape today, outlook tomorrow (1/2)

- Sales of biosimilars in the US lag, as was the case during initial period in Europe and during the initial period of small molecule generic uptake
- The US marketing and payor landscape compounds these challenges
- However, pace of change to accelerate biosimilar approvals, and to simplify acceptance in the marketplace is gaining momentum
  - Dr. Gottlieb and his successor at the FDA has a number of initiatives, from in silico models to correlate PK-PD responses, to accepting clinical data using non-US originator made products, to developing critical quality attributes to reduce the number of lots of the reference product required, to data sharing agreements with foreign regulators, etc
  - These ongoing range of refinements aim to provide overall clarity of the FDA protocol to approve biosimilars, though this is likely to take another year or so
  - FDA has been open to innovative approaches for establishing biosimilarity for eg. Last year, Coherus' pegfilgrastim got the approval based on its analytical and phase I clinical trial data; such innovative approaches will reduce the development cost as well as the timelines
  - Currently, the time to biosimilars review and approval by the US FDA has reduced to 7-9 months, as compared to 18-24 months in 2014
- Market acceptance will take longer to unfold due to a range of inefficiencies embedded in the 'capitalism as practiced by the regulated industry' structure
  - First wave of biologic originators are playing this structure to the hilt and locking in payor groups with long term contracts with highly discounted prices that the initial group of biosimilar companies have not even had a chance to match or exceed
  - The US Government (regulators, policy-makers and judiciaries) will need to rule on how best to balance the societal needs with the current bias towards market forces, even when these forces are compromised by a range of regulatory barriers

Source: Company Reports, MP Analysis

US biosimilars landscape today, outlook tomorrow (2/2)

- With adoption of biosimilars, additional 1.2m patients will have access to biologics, which is currently denied due to high cost
- Payor groups are increasingly taking initiatives to overcome these inefficiencies, where a potential silver lining of giving preference to biosimilars seems to be evolving, almost akin to substitution
  - Approval of next set of biosimilar molecules from the first wave of monoclonal antibodies is likely to trigger a more intensive move in this direction
  - Biosimilar marketers will need to discount their prices well in excess of 60% of the originator price for this effort to achieve a sufficient critical mass
- Competition will only grow even though only a half a dozen companies can be expected to take a lions share of each molecule sales in most major markets
  - Globally, from ~40 companies in 2015, the number of companies that have expanded their biosimilar investments has increased to ~70 in 2018
- Many other companies, who could benefit from creating a sizable biosimilar vertical, still seem to be concerned that status quo will continue and the opportunity will remain constrained, while continuing to require substantial initial investments
  - Smaller companies in biosimilar space inherently face constraints, from amounts they can invest, to number of molecules they can develop
  - Larger companies, many who originated some of the biologics and are now deploying their experiences, and depreciated manufacturing capacity to develop and market the biosimilars of biologics they did not develop, and are still exploring how they can crack open this $40B+ opportunity ($200B originator value at 80% discount) globally
- Pricing strategy and value management are an increasingly important requirement with global price declines and rising competition

Source: Company Reports, MP Analysis

The tide is about to turn in favor of biosimilars as politicians, regulators, payers & patients alike address the barriers

- With 15+ biologics facing patent expiry by 2020, and ~25 more in the coming decade, ~$200+B biologics sales underpin the first wave of biosimilar opportunity, which is forecasted to approach $500B around 2030
- These high priced biologics contribute as much as one-half of healthcare inflation even as only a small fraction of eligible patients can afford these treatments globally
- Proof of equivalence from a number of marketed biosimilars points to substitutability, already being partly practiced by a range of countries and payors
- Recently FDA has finalized interchangeability guidelines favoring the biosimilar manufacturers by -
  - Allowing interchangeable designated products to be substitutable at pharmacy level without the intervention of the prescribers
  - Giving more flexibility to use of global or non-US comparator reference product
  - Clear guidelines to design switch studies where the primary endpoint would be to assess PK/PD rather than focus on efficacy, which in turn will reduce the cost and timeline of clinical trials
  - In parallel, preclinical and clinical requirements are being streamlined to reduce development costs closer to $40m from earlier $120m, which in turn should cut time to approval in half to ~3-years from the 6 – 10 years to-date
- Discounts are rising from 30% to 60%, and high innovative biologics prices ease the path to 80% discounts while still achieving attractive operating margins
- Innovators in many markets are resorting to predatory, preemptive discounting approaching 90% to delay market share loss to biosimilars
- Acceleration of biosimilars adoption is expected to treat some multiple of currently treated patient populations in developed countries, and many more in emerging countries, while at the same time lowering healthcare costs, and thereby fostering next wave of innovations

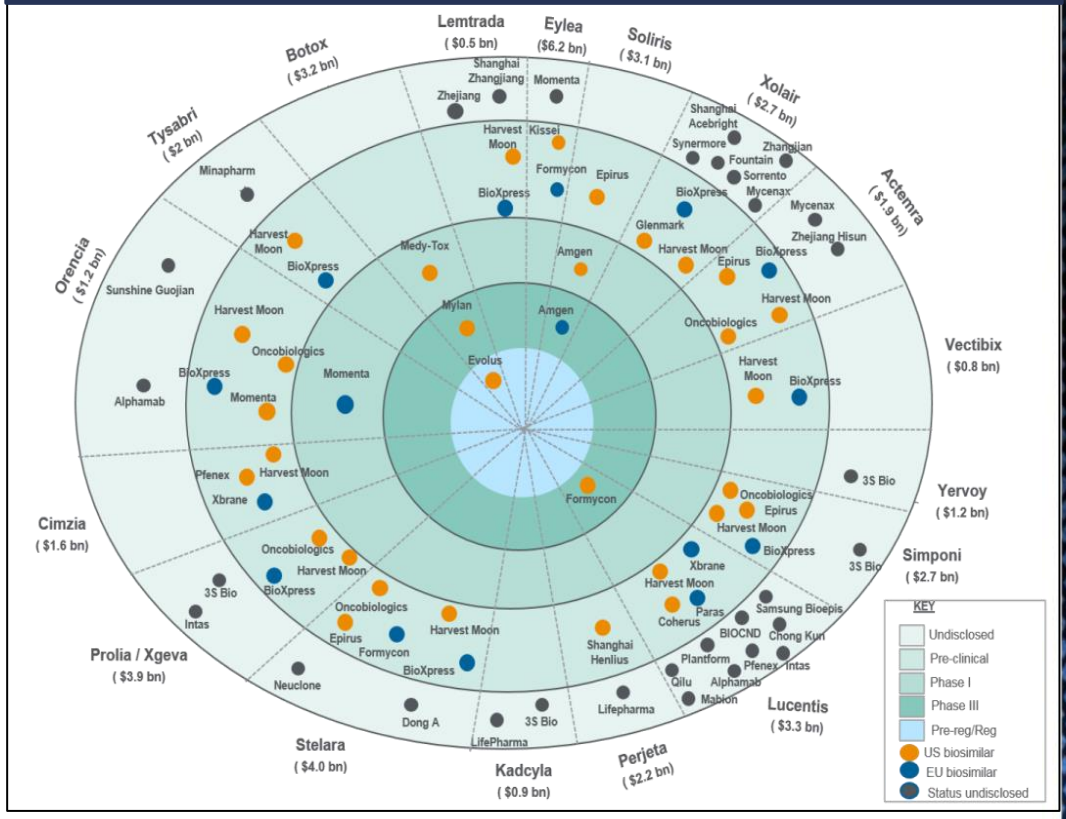
Source: Company Reports, MP Analysis

Growing biosimilars opportunities for the US market

Not too late for the early wave but just in time for the next wave

Competitive Landscape – Early Wave Biosimilars in US				
Biologics	**Marketed**	**Approved**	**Pending Approval**	**Phase III**
Etanercept	-	2	-	1
Filgrastim	2	-	2	1
Pegfilgrastim	3	-	1	-
Epoetin Alfa/Zeta	1	-	-	-
Rituximab	-	2	-	2
Trastuzumab	2	3	-	1
Adalimumab	-	5	-	2
Bevacizumab	1	1	1	2
Infliximab	2	2	1	-
Total	11	15	5	9

Competitive Landscape – Next Wave Biosimilars



- By comparison with EU, biosimilars growth has been slow in the US with ~25 approved biosimilars for 10 originator products, contributing to just about ~$700m in biosimilars sales
- Of the 25 approved biosimilars, only 11 are launched for 10 reference products in US and even fewer have achieved any market success

Source: Company Reports, www.centerforbiosimilars.com, MP Analysis

More companies are likely to join the race for the next wave of biosimilars

- As the regulatory guidelines get clearer and the substitutability becomes a norm, high competitive intensity is expected for the US market with at least half a dozen companies developing a broader portfolio
  - MNCs working on biosimilars are quiet and will only emerge once their products are in the late phase of development
- Ready and "unlimited" access to capital in China ensures that a number of Chinese companies will strive for global biosimilar leadership
- South Korean companies, led by Celltrion and Samsung, are still searching for a global strategy, anchored around their vast manufacturing and development infrastructure; so far they have relied on their western partners for clinical development
- This competitive landscape, combined with near term market uncertainty, calls for consolidation to reduce duplication of efforts
  - Create a JV/partnership to achieve Top-5 leadership, to be enhanced by consolidating from a position of strength

Source: Company Reports, MP Analysis

Over the next decade, biosimilars will mimic the small molecule generics

- Next decade will witness at least a couple of dozens of biologics going off-patent, giving an opportunity to launch 3-5 molecules per year
- Cost of development: Low-double digit millions
- Development requirements: In vitro characterization, BA/BE studies with a small clinical safety study
- Timeline of development: ~2 years
- Competition: Extremely high competition with >10 cos for most of the biosimilars
- Market Penetration: >90%
- Discounts to originator: >80%

Source: Company Reports, MP Analysis

5. Japan is an Attractive yet Unique Biosimilars Market as "Biosame" Knocks at the Door

- Japan Biosimilars Landscape Today - Outlook Tomorrow
  - Japan's biosimilars market is set for accelerated growth
  - Biosimilars uptake varies for each opportunity – Use in DPC hospitals and reimbursement under high cost medical care benefit system are the key factors
- Competitive Landscape Overview - Early & Next Wave Biosimilars
  - Several openings in horizon as major biologics are on verge of patent expiry in Japan
- Regulatory and Policy Landscape
  - MHLW to update a decade old biosimilars guideline by FY2020
  - NHI pricing of "Biosame" key to watch
- Domestic CMO sector likely to grow due to constant supply requirement by PMDA

Japan biosimilars landscape today - outlook tomorrow

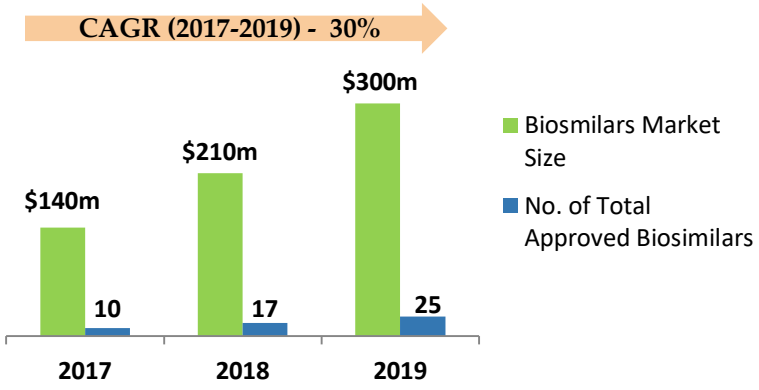
- Japan's biosimilars market is set for accelerated growth, despite the current low base of ~$300m
  - 25 biosimilars of 12 biologics are approved in Japan and have yielded mixed performances
  - Stagnant (Remicade) vs bolstering uptake of Enbrel, Rituxan, and Lantus biosimilars is mainly attributed to product wise difference in the co-pay system, use in DPC hospitals and companies' strong front-end skills to promote
- Japan is a unique yet lucrative market for biosimilars with less stringent regulatory environment
  - In last 3 years, several international drug makers (Pfizer, Amgen, Eli Lilly etc.) entered the Japan market, triggering the growth of the biosimilars market, which has experienced a slow to take off retrospectively
  - A few skipped NHI listing (Pfizer) and stopped prescription (Mochida, Enbrel biosimilars) to better manage constant supply demand, a key requirement by MHLW, implementing the need for mature CDMO in Japan
  - Most of the smaller/mid-size Japanese companies partnered with South Korean firms for the manufacturing know-how, while MNCs followed a either "go it alone" model (Pfizer) or partnered with large Japanese firms
  - Near term - next wave opportunities includes Oncology and Ophthalmology therapy area, while Japanese rising star biotech (JCR) target rare diseases for biosimilars development to fulfill the local needs
- Upcoming regulatory and policy changes in country co-pay system and hospital reimbursements expected to spur the use of biosimilars in the coming time
  - The government has vowed to ramp up its initiatives on the biosimilars front by setting out workshops to educate healthcare providers before giving incentives (FY2019) and update a decade back biosimilars guideline by FY2020
  - New pricing revision (FY2020) of "Biosame" of NESP (originator Kyowa Hakko Kirin approved through its subsidiary without clinical trial) will be important to decide future of mid size/generic biosimilars developers

Note: " Biosame" or an "Authorized biosimilar": Originator's copy of its own biologic

Biosimilars growth is taking off in Japan

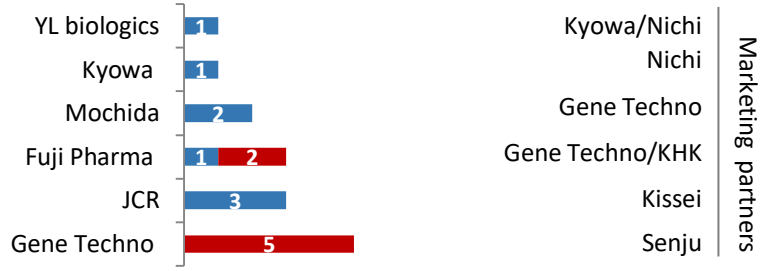
Partnerships with local pharma cos has played a significant role in effective promotions of biosimilars

Expanding Biosimilars Market In Japan

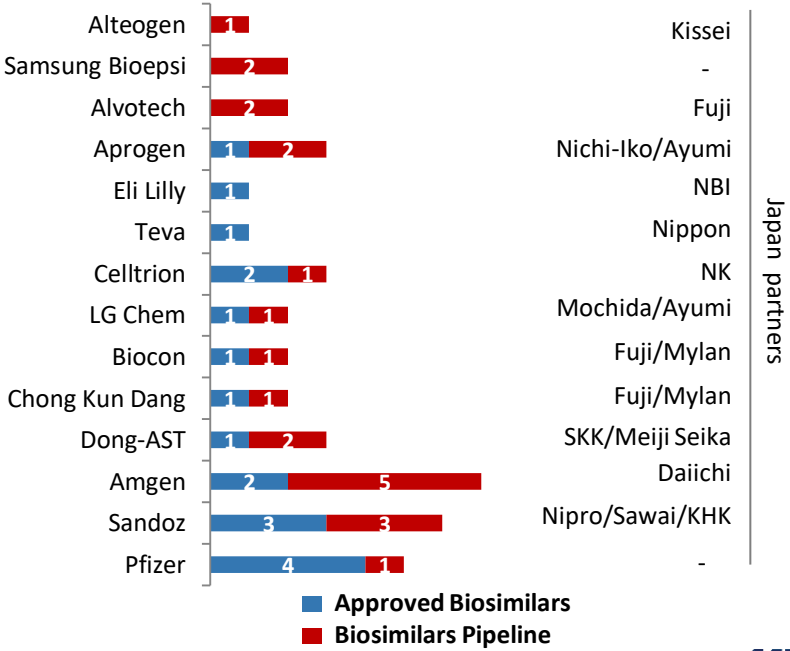


- Presently, 25 biosimilars have been approved for 12 originator products, contributing to about $300m (¥32.4b) sales in Japan
- Most biosimilars in Japan are marketed by mid-sized and generic drug makers; patent expiry of numerous major products has encouraged major international drug makers to enter the foray
- Except Pfizer, all companies used co-promotion/ marketing collaboration with local partners for the front end skill sets (Ayumi, Kyowa Hakko Kirin, Daiichi) in the specific focused therapy area

Partnership Between Domestic Players



Partnership With International Players



Japan approved biosimilars: 2009-2017

Many international and domestic drug developers have joined the biosimilar foray with partnerships with local companies having a front-end capabilities

Biologics (Company)	Therapy Area	Approved Biosimilars			Total Approvals until 2019	Biosimilars in Phase III	Biosimilars in Early Development
		Developers	Partner	Approved Year		Developer/ Partner	Developer/ Partner
Somatropin (Pfizer)	Endocrine, Metabolic and Genetic Disorders	Sandoz	Nipro	2009	1	-	-
Epoetin alfa (Amgen/KHK)	Nephrology	JCR	Kissei	2010	1	-	-
Filgrastim (KHK)	Hematology	Fuji-Mochida Teva Sandoz	Gene Techno Nippon Sawai	2012 2013 2014	3	-	-
Insulin glargine (Sanofi)	Endocrine, Metabolic and Genetic Disorders	Eli Lilly/ NBI Biocon	- Fujifilim	2014 2016	2	-	Sandoz/Gan&Lee
Infliximab (Mitsubishi Tanabe)	Auto Immune Diseases	Celltrion Aprogen/ Nichi-Iko Pfizer	NK Ayumi -	2014 2017 2018	3	Amgen/ Daiichi	-
Rituximab (Chugai)	Auto Immune Diseases	Sandoz Pfizer	KHK -	2017 2019	2	Celltrion/ NK Amgen/ Daiichi	Nichi-Iko & Aprogen
Total					12	5	

Marked Red: International companies
Source: Company Reports, MP Analysis

Uptake of Biosimilars: Low Moderate High

MEHTA PARTNERS

Advisors

Japan approved biosimilars: 2018-2019

Unique biosimilars landscape with the entry of NESP "biosame" and differentiated therapy area expansion like fabry disease

Biologics (Company)	Therapy Area	Approved Biosimilars			Total Approvals until 2019	Biosimilars in Phase III	Biosimilars in Early Development
		Developers	Partner	Approved Year		Developer/ Partner	Developer/ Partner
Agalsidase beta (Sanofi)	Fabry disease	JCR/ GSK	-	2018	1*	-	-
Trastuzumab (Chugai)	Oncology	Celltrion Amgen Pfizer	NK Daiichi Sankyo -	2018 2018 2018	3*	Nichi-Iko & Aprogen	Dong-A/ Meiji Seika (PhI)
Darbepoetin alfa (KHK)	Nephrology	Chong Kun Dang JCR Dong-AST	Fuji/Mylan Kissei SKK	2018 2019 2019	3*	-	YL biologics
Etanercept (Pfizer)	Rheumatology	LG chem/ Mochida YL biologics Kyowa	Ayumi Kyowa/Nichi Nichi-Iko	2018 2019 2019	3*	-	-
Bevacizumab (Chugai)	Ophthalmology, Oncology	Pfizer Amgen	- Daiichi Sankyo	2019 2019	2*	AstraZenica/Fuji -FKB Boehringer	Gene Techno/Mochida (PC) Alvotech/Fuji
Teriparatide (Eli Lilly)	Musculoskeletal	Gedeon Ritcher/ Mochida	-	2019	1*	-	-
Total					13	7	

Drastic increase in the number of biosimilars approvals is likely to expand the biosimilars penetration

* Expected Uptake
Marked Red: International companies
Source: Company Reports, MP Analysis

Uptake of Biosimilars: Low Moderate High

Biosimilars uptake has been inconsistent (1/2)

Patient co-pay dynamic, use in DPC hospitals and a strong commercial partner are main drivers for higher uptake of following biosimilars

Key Factors	Rituximab	Epoetin alfa	Insulin glargine	Filgrastim	Etanercept	Darbepoetin alfa *	Teriparatide *
Made and/or tested in Japan	-	√	-	√	-	-	√
Commercial partner front-end skills	√	√	√	√	√	-	√
Use in DPC hospital	√	-	√	√	-	√	-
Therapy advantage	√ (Shorter treatment)	√ (Disease prevalence)	√ (High device acceptance)	√ (Simplicity of molecular structure)	√ (Administer more often-	-	-
Incentives to hospitals	√	√	-	√	-	√	-
Smaller co-pay/low NHI price benefits	-	√	√	-	√	-	√
No dosage/indication caps with originator	-	-	√	√	√	-	√
Prescribers awareness to use biosimilars	-	-	√	-	√	-	-
Originator strategy to defend biosimilars	Weak	Weak	Strong (Lantus-XR)	Moderate (PEG-Filgrastim)	Weak	Strong (Biosame)	Weak
Future threats	• Gazyva (obinutuzumab) to replace Rituxan	• Biosame • New competitors: Oral HIF-PH	• Next generation molecules & its biosimilars	• Govt boost-medical institutions use • PEG-GCSF entry	• New RA mAbs • Constant supply demand	• New competitors: Oral HIF-PH	• New competitor: Evenity • Auto-injector for Teribone

* Expected uptake

Uptake of Biosimilars: Low Moderate High

Biosimilars uptake has been inconsistent (2/2)

High-cost medical expense benefit system, dosage/indication caps with originator and unstable supplies are major stumbling blocks for below biosimilars uptake

Key Factors	Infliximab	Somatropin	Agalsidase beta	Bevacizumab*	Trastuzumab*
Govt. originator insurance coverage	√	√	√	√	√
Less use in DPC hospital	X	-	-	-	-
Therapy specific factors	X (longer treatment, Brand loyalty)	X (Brand loyalty)	X (Rare disease)	-	X (Constant supply demand- skipped listing)
New drug competitors	X	X	-	-	-
Dosage/Indication caps with originator	X	X	-	X	X
High cost health care system/ No incentives	X	X	X	-	X
Prescribers reluctance to use	X	X	-	-	-
biosimilars company strategy to increase uptake	•Approval via two routes through subsidiary (extra field force) •Increase use in DPC	•Provide real world evidence	•Manufactured using serum-free culture like originator	•Combination strategy - biosimilars + immunotherapy •Robust JP clinical data	-
Originator strategy to defend biosimilars	**Moderate (RemicheckQ)**	**Weak**	**Weak**	**Weak**	**Strong (Fixed-dose combination Herceptin/ Perjeta)**
Future threats	**New competitors**	**New long acting rGHs entry**	**New oral therapy (Galafold)**	**New VEGF inhibitors**	**Roche's Herceptin/ Perjeta entry**

* Expected uptake

Uptake of Biosimilars: Low | Moderate | High

Opening opportunities – Early wave biosimilars

Humira's indication expansion and Skyrizi (risankizumab-rzaa) approval might have a negative impact on the uptake of adalimumab biosimilars, despite fierce competition and large market size

Brand (Company)	Drug	Indication	Launch Year	Patent Exp	Sales FY03/18 ($m)	Estimated Sales FY03/19 ($m)	Biosimilars pipeline
Humira (AbbVie/Eisai)	adalimumab	Rheumatoid arthritis	Jun-08	Exp (2018)	430	460	LG Life Sciences/Mochida (Ph III) Meiji Seika/Dong A (Ph I) Gene Techno Science (PC) Amgen/Daiichi Sankyo* Fujifilm KHK* Alvotech/Fuji pharma* Pfizer*
Synagis (MedImmune)	palivizumab	Respiratory	Apr-02	Exp (2016)	390	320	Gene Techno Science (PC)
Novoseven (Novo Nordisk)	eptacog alfa	Factor VII deficiency	N/A	Exp	61	48	AryoGen (Ph III)
Novorapid (Novo Nordisk)	insulin aspart	Diabetes	Dec-01	Exp (2017)	220	170	Sandoz and Gan & Lee (PC) Biocon/Mylan* Novo Nordisk –authroized biosimilars version by 2020
Humalog (Eli Lilly)	insulin lispro	Diabetes	Aug-01	Exp (2015)	130	99	Sandoz and Gan & Lee (PC)

* Current development status not reported
Source: Company Reports, MP Analysis

Opening opportunities – Next wave of biosimilars

Next wave opportunities to open up as several biologics are on the verge of losing patent in Japan

Brand (Company)	Drug	Indication	Launch Year	Patent Exp	Sales FY03/17 ($m)	Sales FY03/18 ($m)	Estimated Sales FY03/19 ($m)	Biosimilars pipeline
Actemra (Chugai)	Tocilizumab	Rheumatoid arthritis	Jun-05	2019	340	350	380	Mycenax (Plans to apply scientific advice for Japan)
Lucentis (Novartis)	Ranibizumab	Oncology Ophthalmology	Jan-09	2019	180	220	240	CKD (Ph III) Gene Techno Science/Senju (Ph III) Samsung Bioepsi/Biogen (PhIII)
Eylea (Bayer)	Aflibercept	Oncology Ophthalmology	Sep-12	2022	490	560	620	Alteogen/Kissei (PC) Samsung Bioepsi/Biogen (PC)
Erbitux (Merck Serono)	Cetuximab	mCRC	Sep-08	2021	150	150	150	Amgen/Daiichi Sankyo*
Stelara (Mitsubishi Tanabe/Jannsen)	Ustekinumab	Immunology	Jan-11	2021	2	140	200	Alvotech/Fuji* Dong-A/ Meiji Seika (PC)
G-Lasta (KHK/Amgen)	PEG-filgrastim	Neutropenia	Nov-14	2022	170	190	210	Gene Techno Science (PC completed)
Soliris (Alexion)	Eculizumab	PNH aHUS gMG	Dec-10	2020 (PNH) 2023 (aHUS) 2027 (gMG)	NA	NA	NA	Amgen/Daiichi Sankyo*

Paroxysmal nocturnal hemoglobinuria (PNH), atypical hemolytic uremic syndrome (aHUS), generalized Myasthenia Gravis (gMG)

* Current development status not reported
Source: Company Reports, MP Analysis

Evolving regulatory landscape to push biosimilars use

MHLW to update a decade old biosimilars guidelines by FY2020

In 2009, MHLW published guidelines for biosimilars at par with EMA guidelines

- Application submitted to MHLW and then pass to PMDA
- Clinical trials: Similar to EMA, comparative PK/PD studies followed by clinical efficacy and safety trails along with Immunogenicity assessment studies
- Pharmaceutical automatic substitution is not allowed

Unlike the US, no need for a pre-launch "patent dance" in Japan

PMDA will not approve biosimilars before the composition of matter/ second medical use patents expire

JBSA (Japan Biosimilar Association), established in 2016, to study and identify various issues with biosimilars uptake

MHLW guidelines update by FY2020

- MHLW to revise guidelines by FY2020, to support efficient development and increase confidence of physicians on biosimilars quality
- Acceptance of bridging study based on ex-Japan data will significantly reduce the costs of biosimilar development
- "Biosame" from originator approved without any additional clinical trial

MHLW revving up biosimilars drive with educational workshop

- JBSA's ground survey to handle current challenges with biosimilars penetration
- MHLW announced educational workshop for healthcare providers as its first priority, rather than the introduction of a new premium for biosimilars use under the medical fee schedule

Chukiyo's initiatives underway to prepare full-scale entry of major biosimilars with policy changes

"Biosame" NHI- pricing decides further the future of biosimilars development

NHI review prices of medical product every two years

The NHI drug price is the reimbursement price paid to medical institutions and is fixed for each prescription drug approved by the MHLW, unlike EU

High cost medical care system and reimbursement

- Biosimilars are reimbursed at 70% of the original's price
- High cost medical care system, there is a cap on the total amount a patient pays each month, according to age and income
- Most physicians don't have their own opinions on cost-effectiveness, every decision is taken by government
- Lack of incentives to switch to biosimilars under the high-cost healthcare benefit system and public health insurance programs
- Diagnosis Procedure Combination (DPC) with fixed reimbursement fee introduced more than a decade ago for inpatient care

Basic Policy on Economic and Fiscal Management and Reform (honebuto), hammered out in June 2017

Regulatory measures on pricing of biosimilars

- Change in reimbursement policy in next NHI price revision (2020) for biosimilars and "biosame"
- MHLW's new anti-RA measures likely to push further proper use of pricy biologics

Value-based healthcare system to minimize co-pay difference of biosimilars

- MHLW advisory panel recognized value-based healthcare as a central component of its vision in Japan to the year 2035
- Setting prices and reimbursement with cost effectiveness, while integrating health professionals
- Extend DPC system to outpatient care with incentive to use biosimilars
- Government will put measures to incentivize physicians, pharmacy and hospitals for biosimilars use

Honebuto Policy aims to double Biosimilars API by 2020 , while expanding R&D support measures for biologics and biosimilars

Biosimilars are on the verge of breakthrough in Japan

Manufactures

Domestic CMO sector likely to grow due to constant supply requirement by PMDA

- Each companies strong front end foot hold in the specific therapy area along with reimbursement policy of each biologics and innovator strategy for biosimilars, will remain key factors to cherry pick biosimilars portfolio
- Target sizable subgroups of patients whose treatment with biosimilars could hit the co-pay cap (eg. bevacizumab for patients with high body weight) and focus on combination approach (like AZN did for Avastin biosimilars with Fujifilm)
- Domestic CMO sector growth further facilities sharing manufacturing space with industry peers to void supply issues

Regulators/ Reimbursement

Regulatory and Policy measures for pro-biosimilar environment to transform the landscape

- With updated regulatory guideline (FY2020) and spreading biosimilars awareness by giving educational workshops, MHLW aim to double approval of biosimilars in the coming future
- Incorporate biosimilars in the treatment guidelines based on the evidence data and research papers
- Protect biosimilars developers from originator's Biosame for healthy competition become the main hurdle

Healthcare providers

Prescribers recognize the benefits of biosimilars as efficacy/safety concerns fade away

- Work with scientific societies to build biosimilars awareness (e.g. real world evidence and PMS study to show the interchangeability) to diminish quality concerns
- Incentivizing healthcare providers to use the cheaper alternative and treatment scenarios that enables healthcare professionals to choose options based on the settings of each patient

6. Creating a Global Biosimilars Leadership; Combining Complementary Strengths of China and India

- China and India Biosimilars Landscape
  - Policy and regulatory changes are evolving keeping the global standards in mind
- Comparing Biosimilars Landscape Between China and India
  - Research, Development, Manufacturing and Marketing
- What does it take to gain global leadership in Biosimilars?

Biosimilars landscape in China

- The current biosimilars market in China is ~ $1B and is expected to reach ~$6B by 2025
  - ~45 companies have the foundation for biosimilars development with >200 biosimilars in pipeline and at least 25 of them in late stage of development
  - ~10 Chinese companies have partnered with western companies with an aim of establishing global footprint
- Chinese biopharma and financial communities are heavily investing in building state of the art R&D and manufacturing infrastructure with global standards
  - Extensive recruitment of internationally experienced Chinese nationals with a clear understanding of western regulatory and quality standards is underway, showing a clear intent of globalization
  - At a broader level, the positive changes in regulatory and policy landscape have attracted MNC's like BI, Novartis, Pfizer and Merck to make investments and participate in China's growing biosimilars space
- In 2015, Chinese FDA issued new guidelines favoring the biosimilars
  - Revised regulatory guidelines reduces the overall time to market from 5 year to 3 years in addition to accepting the foreign clinical data
  - Several first wave biosimilars included in National Reimbursement Drug List governing the national insurance that covers >60% of the population, at 80% discount to the originator
  - With harmonized western standards being implemented since 2015, biosimilars framework ensuring global manufacturing and quality standards is anticipated in the near future
  - ~200 biosimilars (known as copy biologicals in China) were approved prior to 2015 guidelines

Source: Company Reports, MP Analysis

Biosimilars landscape in India

- The current biosimilars market in India is ~$500m and is expected to reach ~$2B by 2025
  - Currently, ~10 companies have ~20 first wave biosimilars for 11 biologics in late stage clinical development, and ~10 next wave products in early clinical development and the portfolio is rapidly evolving
- Biosimilars franchise of Indian cos primarily focuses on emerging markets while building the foundation to comply with the western regulatory and quality standards
  - Management bandwidth, technical foundation and substantial cash flow generated through emerging market experience will facilitate Indian cos' western market initiatives
- Considering the high investments needed for biosimilars development for Western markets and unpredictable market landscape, it is natural for Indian cos to be cautious
  - Indian cos welcome collaboration with western companies who can provide regulatory and marketing support in addition to financing, while they are still building the required expertise
  - Companies like Biocon, Lupin and Intas have partnered with companies from regulated markets for a handful of products, giving them first hand experience of the regulatory requirements and marketplace, these learnings will be instrumental in shaping their future pipeline
- CDSCO established the first biosimilars guidelines in 2012 and further revised in 2016, with an aim of harmonization with global markets; the key revisions were -
  - Products approved in member countries of ICH can be considered as reference product
  - At least N=100 subjects in test (biosimilars) arm for Ph III clinical trials. Ph III may be waived based on comparable quality, non-clinical and PK data to the reference product in Ph I
    - If the Ph III is waived, a single arm Ph IV post market study is mandatory with N=200 subjects within 2 years
  - ~50 biosimilars were approved prior to 2016 revised guidelines

Note: CDSCO - Central Drugs Standard Control Organization
Source: Company Reports, MP Analysis

Biosimilars landscape – China vs. India

- Global biosimilars sales are expected to reach $40B by 2025, as multiple initiatives converge to increase biosimilars marketplace adoption
  - Biosimilars market is relatively matured in EU and while US has been a laggard, it is catching up
    - High competitive intensity is expected for the US market as the evolving regulatory guidelines are favoring biosimilars and substitutability will soon becomes a norm
- Chinese companies' maturity for the global markets is evolving with the current regulatory landscape favoring biosimilars
  - In June 2019, trastuzumab biosimilars developed by Henlius was the first biosimilar from China to be accepted for review by EMA for market authorization in the EU
- While the overall investments on biosimilars in India have been limited, ~10 Indian companies are taking the necessary yet measured steps to gain global biosimilars leadership
  - Indian companies, combined have two biosimilars approved in the US (Biocon), four in EU (Biocon, Lupin and USV) and one for Japan market (Lupin) with at least 5 biosimilars in global phase III and at least half a dozen more in early clinical development
- Chinese and Indian companies' complementarities have already begun to extend to the emerging markets
  - Cipla has partnered with Henlius for its trastuzumab biosimilar, where Cipla will register the product and commercialize in select countries in Asia Pacific and Latin America region
- Collaboration between a top tier Indian and Chinese co, leveraging complementary skillsets has the potential to attain global leadership in biosimilars space, determining the real success
  - While Indian cos bring broader portfolio, western regulatory experience and marketing front end and emerging market experience, China has the access to capital, technical skill sets and marketing experience for China market

Source: Company Reports, MP Analysis

Biosimilars regulatory & policy guidelines

Parameters	Current Status - China	Current Status - India
Regulatory Guidelines	• Biosimilars are subject to the new drug approval pathway, but their technical reviews will follow the new biosimilars guideline • A reference product must be approved in China • Increased transparency in the review process and acceptance of foreign clinical trials data • Stringent quality control measures that requires clinical trial site inspection report - In one year, 1622 applications were rejected after CFDA site inspection with incomplete data • Faster approval by NMPA with biosimilars time to market of 2-3 years	• CDSCO created biosimilars guidelines in 2012 that were revised in 2016 to comply with global standards • The Reference Biologic should be licensed / approved in India or ICH countries • At least 100 patients are required in test (biosimilars) arm for a Phase 3 study, which was not specified previously • Phase 3 waiver is considered subject to the quality of data however, a Ph IV post marketing data in at least N=200 patients should be submitted within 2 years
Chinese govt. Policy	• New National Reimbursement Drug List (NRDL) became effective in 2017 to regulate pricing • >60 percent of the population is covered under the national insurance coverage plan • NRDL includes some of the first wave biosimilars and will consider adding more to the list • Marketing Authorization Holder need not be the owner of manufacturing plant • Joined ICH in 2017	• National Pharmaceutical Pricing Authority (NPPA) controls the biosimilars pricing in India • No national insurance coverage provided by the government • Limited measures taken to educate the relevant stakeholders on biosimilars
Originators' Influence	• Uptake of originator biologics is low due to high cost • All the innovator biologics are not approved in China posing a challenge for biosimilars development	• Only originator biologics are available at discounted price in the government hospitals • The biologics penetration is low due to high cost of the originator which the patient pays out of pocket

Source: Company Reports, MP Analysis

Policy & regulatory changes set the foundation for biosimilars market expansion

Parameters	Implications - China	Implications - India
Pricing	• Mandatory usage by many hospitals along with high competition will lead to availability of biosimilars at higher discounts and increase the market penetration	• Price competition in the biosimilars market largely exists at government hospitals but do not benefit the patients • Transparent pricing is yet to be implemented as overall penetration of biosimilars remain low
Manufacturing Infrastructure	• New policies will encourage more clinical trials site initiation and CRO business • A large number of companies with new and state-of-the-art facilities can potentially make China a global manufacturing hub for biosimilars • Marketing Authorization Holder not requiring to own a manufacturing plant will encourage small biotechs to explore biosimilars space	• Some of the Indian pharma companies have the manufacturing infrastructure with global compliance and already supplying for clinical development/commercial use in the West
Market Acceptance	• The biosimilars have been well accepted by the key stakeholders • More competition from companies within and outside China will take a significant proportion of originator's market share	• Biosimilars acceptance is low due to low access and lack of awareness among the prescribers and patients • The government is trying to offer national coverage with the Aayushman Bharat program and having biosimilars covered under this program
Market Expansion	• Increasing number of biotech companies are partnering with international companies to expand globally • ~200 biosimilars clinical trial applications have been approved in China alone	• Only ~15 cos have expanded into the biosimilars space considering the high initial investments • ~10 companies have late stage biosimilars in their pipeline for domestic as well as global markets
M&A/ Partnership Focus	• China is an attractive avenue for global companies, although the system mandates the foreign companies to have a Chinese partner • High number of partnerships in the coming decade will give global exposure several Chinese cos., while addressing the unmet needs of the domestic markets	• Most of the Indian companies are exploring opportunities in emerging markets • A handful of companies have entered into a strategic partnerships with companies in regulated market

Source: Company Reports, MP Analysis

Late phase biosimilars in China (1/2)

Biologics	Biosimilar Companies	International Partner	Phase of Development	Global Revenue (2017)	China Revenue (2017)	Approved (US)	Approved (EU)	Total biosimilars in development in China
Rituximab (Rituxan, Roche) Listed on NRDL	Henlius (fosun)	-	Approved	$7.2 B	$258 m	1	6	6
	Innovent	Eli Lilly	III					
	CP Guojian	-	III					
	Sinocelltech	-	III					
Adalimumab (Humira, AbbVie)	Innovent	Eli Lilly	PA	$18.4 B	$50 m (low uptake because of High cost) 2017	3	7	13
	Bio Thera	-	PA					
	Henlius	-	III					
Infliximab (Remicade, Janssen)	Biomabs	Only in 2017, Remicade was approved in China		$7.15 B	$30 m	3	4	2
	Hisun Pharma							

Source: Company Reports, MP Analysis

Late phase biosimilars in China (2/2)

Biologics	Biosimilar Companies	International Partner	Phase of Development	Global Revenue (2017)	China Revenue (2017)	Approved (US)	Approved (EU)	Total biosimilars in development in China
Etanercept (Enbrel, Amgen)	Simcere	-	III	-	-	2	2	4
	Hisun Pharma	-	III					
Trastuzumab (Herceptin, Roche) Listed on NRDL	Henlius	-	PA	$7.44 B	$159 m	5	5	9
	Simcere	-	PA					
	Genor Biopharma	-	III					
	Walwax	-	III					
Bevacizumab (Avastin, Roche) Listed on NRDL	Qilu	-	III	$7.44 B	$70 m	2	2	18
	Innovent	Eli Lilly	PA					
	TOT Biopharma	-	III					
	Henlius	-	III					
	Bio Thera	-	III					
	Anke Biotechnology	-	III					
	Luye Pharma	-	III					

Source: Company Reports, MP Analysis

Late phase biosimilars in India

Active Ingredient	Company Name	Phase of Development	Global Revenue (2017)
Bevacizumab*	Amneal	Phase III	$7.44 B
	Dr. Reddy's	Phase III	
Denosumab	Reliance Life Sciences	Phase III	$5. 40 B
Ranibizumab	Reliance Life Sciences	Phase III	$1.90 B
	Intas	Phase III	
Trastuzumab*	Reliance Life Sciences	Phase III	$7.44 B
	Glenmark	Phase III	
Omalizumab	Reliance Life Sciences	Phase III	$2.5 B

Note: *Biosimilars already marketed in India by other companies

Source: Company Reports, MP Analysis

Biosimilars landscape overview - China vs. India

Parameters	China	India
Regulatory body	CDE-NMDA	DBT-CDSCO
Regulatory guidelines	Effective since February, 2015	Effective since August, 2016
Reference product use	NMDA/Foreign approval plus	EMA or FDA approved
No. Of controlled clinical trial centers	low	low
Development and approval timeline	2-3 yrs	2-3 yrs
Interchangeability	Not addressed	Not addressed
No. of biosimilars approved prior to revised guidelines	~200	~50
No. of biosimilars approved with revised guidelines	1	~15
No. of biosimilars companies	~45	~15
Companies with FDA/EMA approved facilities	~5	~10
Companies with potential for FDA/EMA manufacturing approval	10	15
Population covered by health insurance	>60%	~15%
Number of deals (2013-2019)	~15	~20

Source: Company Reports, MP Analysis

What does it take to gain global leadership in biosimilars?

Where do china and India stand?

Research

Parameters	China			India		
	Current	Expected	Explanation	Current	Expected	Explanation
No. of companies that have at least one biosimilars in the pipeline	◑	◑	• At least 45 companies	◔	◑	• More companies are expected to explore biosimilars space as the landscape matures
Pipeline	◔	◑	• Few companies with broad biosimilars portfolio • However, portfolio expansion expected going forward	◑	◕	• At least half a dozen companies with broad portfolio • Portfolio expansion likely to continue going forward
Skilled labor/Technical knowhow	◑	◕	• Retaining skilled labor plus recruiting internationally experienced Chinese nationals • Increased focus in academia research	◔	◑	• Dearth of experts with global experience • Likely to leverage global network for IP, regulatory and technical support

◔- Low ◑- Medium ◕- High

Source: Company Reports, MP Analysis

What does it take to gain global leadership in biosimilars?

Where do china and India stand?

Development

Parameters	China			India		
	Current	Expected	Explanation	Current	Expected	Explanation
Access to capital	◑	◕	• Easy availability of public or private fundings • Clear and a relatively easy path for company listing on Chinese or Hong Kong stock exchange	◔	◔	• Public or private funding is not available easily • Situation unlikely to improve in the near future
Government support	◑	◕	• Major healthcare reforms are undertaken by the government • Price control by NRDL	◔	◔	• No mAbs/biosimilars are on Reimbursement Drug List in India • No incentives for biotech industry
Western regulatory knowhow	◔	◑	• Limited western regulatory and market experience at present • Recruitment of senior management with Western experience underway	◑	◕	• Current expertise in small molecules • Few cos have first hand regulatory and market experience from the biosimilars partnership with Western cos

◔- Low ◑- Medium ◕ -High

Source: Company Reports, MP Analysis

What does it take to gain global leadership in biosimilars?

Where do China and India stand?

Manufacturing

Parameters	China			India		
	Current	Expected	Explanation	Current	Expected	Explanation
Quality standards	◔	◕	• Development of infrastructure with global quality standard underway • Global partnerships will further help to improve quality standards	◔	◑	• ~10 companies supply products to the West for clinical development or commercial use • These cos will further benefit from partnerships with global companies
Innovation/ Biobetter capabilities	◑	◕	• Most biotech companies focus on innovation and biobetters • Adoption of innovation will only increase in the future	◔	◔	• Limited initiatives in innovation and biobetters so far • This trend is likely to continue in the near future
Infrastructure with FDA/EMA approval	◔	◕	• <5 cos seem to have FDA/EMA approved facility • This number will increase drastically considering the investments in infrastructure	◑	◑	• At least10 Indian cos have received USFDA/EMA approvals till date, with very few additions expected

Source: Company Reports, MP Analysis

◔- Low ◑- Medium ◕- High

What does it take to gain global leadership in biosimilars?

Where do China and India stand?

Marketing

Parameters	China			India		
	Current	Expected	Explanation	Current	Expected	Explanation
Domestic market potential	◑	◕	• Current domestic market is $1.5B and is expected to reach $5.5B by 2025	◔	◑	• Current domestic market is $500m is expected to reach ~$2B by 2025
Biosimilars approval by FDA/EMA	◔	◑	• None approved by the West so far; Henlius is in the process of getting EMA approval for Rituximab	◔	◑	• Started getting approvals in developed markets; 2 in the US, 4 in the EU and 1 in Japan
Companies with registered products in the US	◔	◑	• ~35 companies have product registration in the US • Very few (<10) cos have marketing front end	◑	◕	• >60 companies have products registered in the US with at least 20 companies having a marketing front end
Global deals in last 3-5 years	◔	◕	• ~15 deals to date primarily to develop biosimilars for China market • Deals with global focus are likely to increase in the near future	◑	◕	• ~30 deals so far to co-develop biosimilars for global market • Future partnerships will depend on the Indian cos' inclination towards investing in biosimilars space

◔- Low ◑- Medium ◕- High

Source: Company Reports, MP Analysis

Conclusion – together, India and China has what it takes to gain global biosimilars leadership

Parameters	China	Comments	India	Comments
Broad Portfolio	Mostly first wave Alphamab -5 Innovent - 3 Henlius - 7 3SBio - 4	◔	First & Second wave RLS - 30 Biocon - 28 Zydus - 18 Lupin - 8	◕
FDA/EMA Approved manufacturing facilities	Innovent, Henlius , 3SBio	◔	Biocon, Zydus, Dr. Reddy's, Lupin, Intas, Aurobindo, etc.	◑
Western regulatory experience/presence	Very few cos have sales and marketing front end	◔	>20 companies have sales and marketing front end	◕
Capital Access	Availability of extensive private, public and government funding	◕	Limited funding for biosimilars; cautious approach by India cos further limit the funding	◔
Skilled Labor/Technical Know How	Expats with global experience recruited; focus on academia	◕	Limited availability of skilled labor	◔
Innovation/Biobetter capabilities	Key focus on innovation	◕	Most Indian cos are still focusing on generics	◔

◔- Low ◑- Medium ◕ - High

Source: Company Reports, MP Analysis

MEHTA PARTNERS

Advisors

Thank you