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Biosimilars promised the Moon but did not deliver

Were we expecting too much and is it time to be optimistic again?



Source: Suzanne M. Sensabaugh. Biological generics: A business case (2007) Journal of Generic Medicines 4 , 186-199, * MAT 03/2012



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Biosimilars are approaching a turning point

Positive moves are apparent, but still much has to change





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This trend is supported both from demand and supply drivers

Mature economies look at them in the attempt to stem costs; emerging ones to ensure access and sustainable growth

Demand side

- Cost-saving lever for mature economies experiencing increasing pressure on resources
- ✓ Growth engine for emerging economies while ensuring broader access to medicines and sustainability
- ✓ Regulatory framework still fragmented across regions
- Exposure to biosimilar real world evidence limited to a few areas (mostly Europe)



Supply side

 ✓ Increasing inflow of capital and "branded" capabilities through BigPharma and more "unusual" players (Samsung, Fujifilm, GE Healthcare)

 ✓ Increasing specialization along the value chain unlocking the potential of successful partnerships

 ✓ Biologics capacity oversupply, pushing manufacturers to find ways to leverage unexploited capacity



Biologics growth is nearly double that of total pharma

Such a trend is putting additional financial pressure on healthcare budget, whereas for PharmaCos represents a great opportunity



Biologics – Share of sales 2,6%5,4% 48,5% 21,9% 9,2% 12,5% ■ F7 Canada EU5 ■ JAPAN Others US **Biologics – Share of growth** 4,3% 11,6% 49,5% 13,3% 9,2% 12,2%



Source: IMS Health, MIDAS, MAT 09/2012

Three geographical clusters arise

Emerging economies anticipated to be a potential growth driver due to local policies and "biosimilar" attitude



Source: IMS MIDAS, 2006-11, *biosimilars in emerging economies have not gone through a thorough screening like in Europe



The global regulatory framework is still quite heterogeneous

Some key emerging markets still lag behind in terms of regulatory guidance



Current hurdles to global biosimilar market

Patient ethnicity, Opportunity to leverage evidence from other geographies, PK testing, Clinical testing requirements, Interchangeability



Biologic market is still at its early stage in emerging markets

Bioclusters are rapidly emerging in the major Asian emerging markets and will fuel growth of the biopharmaceutical sector in this area







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In Europe, biosimilar uptake exhibits different paces

A few countries have reached or approached the maturity stage





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Similar variations can be observed at therapy area level

Biosimilar filagrastim resembles generic performance in some countries (UK, France, Germany)





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Commodity or differentiated?

Stakeholder landscape – payer-driven vs. multiple influencers – and treatment cycle are the key determinants

Filgrastim uptake Somatropin uptake SU 09/2012, quarterly SU 09/2012, quarterly Commodity market Differentiated market 100% 100% SU SU 80% 80% % Uptake, % Uptake, 60% 60% 40% 40% 20% 20% 0% 0% 8 5 Τ2 13 4 13 Γ6 T11 T12 T13 T13 T14 T15 T15 Ę 10 FRANCE GERMANY -----ITALY FRANCE GERMANY -UK SPAIN -SPAIN —UK

- ✓ Payer-driven market access (e.g. Tender, stepwise algorithms)
- ✓ Price-driven competition
- ✓ Acute treatment and/or frequent cycling among therapies

Source: IMS MIDAS, 09/2012

- ✓ Complex stakeholder landscape with higher physician influence
- Competition based on multiple marketing levers
- ✓ Chronic treatment and/or long therapeutic cycles



-ITALY

Biosimilars have in some cases generated expanded access

As shown by G-CSFs, biosimilars improve access to therapies based on efficacy and costs



UK case study



- Physicians moved G-CSF back in 1st line cancer treatment due to lower biosimilars cost
- G-CSF prevents hospital readmission due to infections
- The volume effect has both created new market and cannibalized the share of follow-on products (e.g. peg-filgrastim)

Source: IMS MIDAS, MAT Q4 2010, NHS. *t-1 =100%, t0 = year of biosimilars introduction

← France ← Germany ← Italy ← Spain ← Sweden ← UK



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Although the opportunity for volume expansion is therapy area (and geography) dependent

- Largest volume expansion potential undoubtedly in pharmerging, but probably at a much lower price point
- Europe has lower and also variable biologic uptake relative to US
- US has highest penetration of biologics/head – least volume expansion potential?
- Volume expansion potential will also be affected by introduction of new, better innovative therapies (eg pertuzumab, Roche)

Erythropoietin for renal dialysis

Oncological biologics always have the

competitive threat of innovation to reduce volume for biosimilars

Human Growth Hormone and other orphan drug biologics show typically show high percentage of available patients treated

Erythropoetins for oncology

Oncological biologics in

some European countries (eg UK) show significantly lower levels of use than elsewhere on cost grounds

Filgrastim has already shown price elasticity

Biologics for autoimmune show highly variable levels of use across patient populations, driven by access in Europe (>5% of patients to >30% across Europe*)



In Spain, biologics represent one of the major cost drivers

However, biosimilars still represent a minimal portion of the total market



BRANDED BIOLOGICS BIOSIMILARS

Source: IMS MIDAS, MAT 09/2012



Payers and policy-makers are rising as biosimilar advocates

Biosimilar strategies and business models will be another critical factor to shape the future scenario

Stakeholder drivers

<i>Payer / Government</i>	 Increasing pressure on public/private budgets Ensure safety and clinical efficacy of biosimilars Leverage macroeconomic growth through biosimilars (EM) Broaden access to life-saving drugs
Patient	 Broad access to life-saving / disease-modifying drugs Safety profile of biosimilar drugs Access to affordable therapies (EM, partly US)
Physician	 Safety and clinical efficacy concerns Need to build learning curve on biosimilars Different influence depending on therapy area (likely to be higher for the new wave)
Aspiring player	 Massive capital invested on biosimilars BigPharma bringing in R&D and manufacturing capabilities as well as brand equity Growing specialization along the value chain (CRAMS providers) and availability of new leading technologies
Originator	 IP challenges to delay/block biosimilar entry (e.g. Enbrel in US) Timely implementation of lifecycle management strategy (e.g. Roche with HER2 franchise) Leverage dual brand strategies / licensing in developing markets
EM = emerging markets	

Impact on biosimilars market





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Overall these events lean closer to the \$25 billion 2020 scenario

The verdict on the new wave of biosimilars will act as a cornerstone for this market

~ \$25 Bil	<i>Core scenario drivers 2020</i>	~ \$11 Bil		
Latest US biosimilar guidance setting a clearer framework for biosimilars and leveraging totality of evidence approach	US uptake	Limited uptake in the US due to unclear regulation favouring innovators		
Latest law provisions striving to promote harmonization of regulatory standards and pivotal role of emerging countries	Emerging markets	Moderate spread of biosimilars along with EM not emerging as a leading exporter due to quality standards		
Accelerating uptake in EU, including typical laggard countries as they are under increasing financial pressure	Europe	Growth hormones still exhibits limited uptake rates		
Successful development of some of the key biological blockbusters (<i>infliximab, rituximab, trastuzumab</i>)	Technology, second wave	Extension of Enbrel's patent coverage to 2028 (US only). Disputes on Humira		
Significant volume effect on biologics consumption (as exhibited by gCSF) replicated in other therapy areas	Volume effect	Limited volume effect as biosimilars are exclusively used as a cost-containment tool		
Increasing manufacturing efficiencies and large competitive arena trigger price competition and promote uptake	Competitive dynamics	Pfizer calling off deal with Biocon may signal potential difficulties and delays in the development of biosimilars		



Among the new TAs, anti-TNF and MAbs are the key ones

Along with insulins, another key investment area for biosimilar players, they account for more than 40% of the overall biologic market





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Twelve compounds will present a US\$ 67 billion opportunity

All these products will lose patent protection by 2020, but Enbrel whose US patent has been extended until 2028

Global Sales (MAT 09/2012), US\$ billion

	8.1		Adalimumab (Humira)	2018
	7.3		Etanercept (Enbrel)	2015
	7.1		Infliximab (Remicade)	2014
	6.2		Insulin Glargine (Lantus)	2014
	5.9		Rituximab (Mabthera)	2013
	5.3		Bevacizumab (Avastin)	2019
5	5.0		Interferon Beta-1A (Avonex, Rebif)	2012
5	.0		Trastuzumab (Herceptin)	2015
4	.9	Total	Insulin Aspart (Novomix, Novorapid)	2014
4.3	3	~ US\$ 67	Glatiramer Acetate (Copaxone)	2017
4.3	3	billion	Pegfilgrastim (Neulasta)	2015
4.0			Ranibizumab (Lucentis)	2016
0		5	10	Not considered such as Epoeti

US expiry date

2016

2028 (extended)

EU expiry date

Not considered existing biosimilars such as Epoetin Alfa expired in EU, but still patent protected in US



Source: IMS MIDAS, 09/2012, IMS Patent focus

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Monoclonal antibodies dominate the biosimilars pipeline

Biosimilars pipeline by class

Class	Preclinical	Phase I	Phase II	Phase III	Prefiling/Pending
mAb immunomodulators	55	4	4	2	1
Cytotoxic Mabs	28	5	1	3	0
Other hormones (excl. insulins)	19	3	1	6	0
G-CSF	16	1	3	6	1
Insulin	14	4	3	3	1
Others (enzymes, BCF)	15	3	2	0	3
Interferons	14	3	3	1	1
Erythorpoietin	14	1	1	5	0
Immunomodulators	8	1	1	2	1
Total	183	25	19	28	8

Source: FirstWord September 19th 2012



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Among the core areas, anti-TNF are at higher risk of erosion

Uptake patterns will vary across geographic clusters, e.g. biosimilar insulins may perform better in emerging countries



Positioning of upcoming biosimilars



The next wave will be pivotal to determine future scenarios

The way the industry as a whole will pave the way to it and continue building the learning curve will shape the uptake through 2020





Biosimilars have been a hot topic in the last 12-18 months

The landscape is becoming over-populated. Is there a market for everybody?





Original manufacturers will employ a range of defence approaches to contain the impact of biosimilars

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Fight on price, if you are		
Moderate risk to original brand	•	HgH has shown that brand loyalty can protect under certain circumstances – for a period of years
Fight on price even where discounts are low: ensure that small price discounts do not let biosimilars gain significant traction	•	Current experience has not been of interchangeable biosimilars (USA), or substitution (Europe). Either is likely to be a
t	Fight on price, if you are repared to go to commodity levels Moderate risk to original brand Fight on price even where discounts are low: ensure hat small price discounts do not let biosimilars gain significant traction	 Fight on price, if you are repared to go to commodity levels Moderate risk to original brand Fight on price even where discounts are low: ensure hat small price discounts do not let biosimilars gain significant traction

Willingness to use (physician/patient acceptance)



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New biologics represent a threat for upcoming biosimilars

When engaging stakeholders, the biosimilar value proposition should include both the originator and follow-on biologics in the same TA





As biosimilars are mainly copies, speed to market remains key

Going forward, while the scientific aspects will remain a basic prerequisite, commercial models could drive differentiation at local level



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Go-to-market models are soon expected to transform

The evolving competitive arena and more complex biosimilars portfolios to manage will drive the transition



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Biosimilar go-to-market evolution





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