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Herceptin biosimilars – the real prize remains Europe

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Biocon and Mylan may have achieved a world first in launching a generic version of one of Roche's biggest-selling cancer drugs, but copycat versions of Herceptin in India, where sales are only estimated to reach about $21m, will do little to disturb the sleep of Swiss executives.

The real wake-up call will come with the company that manages to get approval in Europe, where there is a clear biosimilar pathway and an opportunity to eat into the multibillion sales the drug generates in the region.

Herceptin loses patent protection in July 2014 and having smelt blood there are a number of sharks circling in European waters (see table below).

Since 2007 the European Medicines Agency (EMA) has authorised 16 biosimilars and refused approval for two. While the majority of these have been in the easy-to-copy categories of erythropoietins and growth hormones, last year the EMA granted authorisation for what many saw as the first "proper" biosimilar when it gave the nod to Hospira and Celltrion's Inflectra/Remsima, a version of Johnson & Johnson's Remicade (*EU opens door to biosimilar antibodies, June 28, 2013*).

So, with a proven willingness to provide patients with cheaper alternatives to branded biologicals in Europe, and the US biosimilars approval pathway littered with pitfalls, when the European patent for Herceptin does expire there will be a rush to gain approval.

Diminishing returns

Last year European sales of Herceptin hit $2.1bn, and as with the small molecules there will be rapidly diminishing returns for those furthest away from the market.

Late-stage Herceptin biosimilars			
Market status	**Product**	**Company**	**Target markets**
Approved in India and South Korea	CANMAb/Hertraz	Mylan/Biocon	US, Canada, Japan, Australia, New Zealand & Europe (Profit share); RoW (co-promotion)
Approved in South Korea	CT-P6	Celltrion	WW ex USA, Europe, Japan, Australia, New Zealand & Canada; USA, Europe, Australia, New Zealand & Canada (royalties); Japan (co-promotion with Nippon Kayaku)
Phase III	Trastuzumab	Amgen/Actavis	WW, royalties (Actavis)
Phase III	Trastuzumab	Hospira	US, Europe, Australia, New Zealand & Canada
Phase III	PF-05280014	Pfizer	WW
Phase III	Trastuzumab	Synthon	WW (royalties)
Biosimilar (ex-US only)			
Phase III	Trastuzumab	Novavax	India
Phase III	Trastuzumab	Cadila Pharmaceuticals	India
Phase III	Trastuzumab	Biocad	Russia, Ukraine, Belarus, Kazakhstan, Moldova, Armenia & Azerbaijan

Having actually launched a version of Herceptin Biocon might seem the most likely candidate to clean up in any European tussle. Rightly or wrongly there are concerns that the regulatory hurdles that Biocon has managed to jump for Indian approval might not stand up to European scrutiny.

Indian biosimilar guidelines are supposed to replicate those of the EMA, but the fact that the drug has not been tested outside India could count against it.

So perhaps best positioned so far is Celltrion, which last week gained approval for its version of Herceptin, Herzuma, in Korea. The company has also conducted global trials of the drug, which should play well in any possible European filing. Celltrion will launch Herzuma in Korea later this year at a 30% discount to Herceptin.

The group’s seeming expertise at creating and launching biosimilars is one of the reasons why there is growing speculation that Celltrion could be the target of a buyout from big pharma companies looking to boost their presence in this field. Both AstraZeneca and Roche have in recent weeks been named as likely suspects for a takeover bid after chairman Seo Jung Jin said last year he was willing to sell his stake in the company.

But while Celltrion might have the most approved biosimilar monoclonal antibodies under its belt and a phase III version of Rituxan in development, it is its old partner in crime Hospira to which analysts are willing to provide forecasts for generic versions of Herceptin, pencilling in a European launch in December.

Getting in early

Investors may be betting on Hospira to crack Europe first, but there are other challenges from bigger, more established names, such as Amgen, which had started clinical trials of generic trastuzumab in early-stage disease as part of its biosimilar collaboration with Actavis.

But Amgen, which appears to be primarily targeting the US, has run into development problems and has been forced to suspend its Lilac trial temporarily owing to delays in the availability of biosimilar trastuzumab.

However, when it does get started again, studying the drug in early disease should stand it in good stead given that 75% of women starting Herceptin are in this rather than the metastatic setting.

Others developing biosimilar Herceptin, including Celltrion and Hospira, have studied metastatic patients and will most probably use the data as a reference for how the drug would perform in early-stage HER2-positive breast cancer.

The hope is that this will be enough under EMA guidelines; otherwise the winner in the European battle for Herceptin sales might not cross the finish line for some years yet.

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