INNsight article by Peter Wittner, Interpharm Consultancy, January 2012

Peter has been in the pharmaceutical industry for 30 years of which the second half has been mainly in the areas of generics. He has worked for the former Evans Medical and then Norton Pharmaceuticals (now part of IVAX) where he was responsible for European Sales & Marketing. After leaving Norton Peter set up his own consultancy in 1993 and operated independently until 1996 when he joined the Indian company Ranbaxy to set up the infrastructure of their new UK subsidiary and spent two years with them. For the last 7 years he has been back doing consultancy and specialising in the field of generics.

Biosmilars – what happened?

There was great hope (or even hype?) over the last few years that manufacturers of Biosimilars would carve out nice chunks of the originator's sales of biological products in the same way that generics have done. You know the scenario – a patent expires, twenty generic copies leap in and within a few weeks the price has crashed 90% and 90% of the market becomes generic.

Only it hasn't quite worked out that way for Biosimilars.

On the other hand, the Biosmilars' market has not been a disaster either, just not quite as exciting as people had expected. So how has reality diverged from expectation – what lies behind it?

As far as Europe is concerned, the question of interchangeability has been significant. The inability of pharmacists to substitute one biosimilar in place of another or in place of the original has acted a powerful brake.

With respect to the US, the key issue has been the lack of a regulatory pathway for Biosimilars even though two years have now passed since Obama signed the relevant legislation into existence. Nevertheless, the big success in the copy biological area has been Sandoz USAwith its Enoxaparin copy of the Sanofi product Lovenox that, interestingly, was not approved through any biosimilars route; rather it went through what is in effect a biological ANDA route.

Just to illustrate the level of success that Sandoz has enjoyed, it is reported that generic Enoxaparin generated sales of well over US$1bn in its first year. Sandoz and its partner Momenta also managed to obtain an injunction against the only other generic competitor, developed by Amphastar with its commercial partner Watson, on the grounds of patent infringement thus keeping the market to themselves.

In an interesting related development, at the time that the FDA announced its approval of the Amphastar product Sanofi announced the launch of an "Authorized Generic" version of Lovenox through its Winthrop subsidiary. This reached the market in October – and was withdrawn by December! Why? Well it seems that when there was a risk of increased competition and a more fragmented market, Sanofi thought that it had better try to get a slice of the generic action. When that risk disappeared with Momenta's success in obtaining a restraining injunction, Sanofi had a rethink. It presumably decided that there was no point in muddying the waters by unnecessarily competing with itself and announced the withdrawal of its own generic.

The withdrawal was announced as follows "*November 30, 2011 -- Winthrop U.S., a business of Sanofi-Aventis U.S. LLC, announces discontinuation of distribution of the Winthrop Enoxaparin Sodium Injection, the authorized generic of Lovenox (Enoxaparin Injection). This action is in response to an ongoing assessment of market conditions and is limited to this product only."* This is nicely vague and gives no clues as to the real reasons for the withdrawal.

Aside from all the Enoxaparin action though, not much seems to be happening on the Biosimilars front in the US. So back to Europe where it all started.

Europe led the way with the EMA producing the first guidelines on Biosimilars in general and then going on to produce specific guidelines for various classes of products. When combined with patent expiries this produced waves of Biosimilar approvals – for example HGH (Human Growth Hormone) in Quarter 2 of 2006. This was followed by a wave of EPO products in Quarter 3 of 2007 and Filgrastim / G-CSF product in 2008.

This should, in theory, mean that by now, based on the generic precedent, most of the HGH market would be dominated by copy products, but this has not happened. There are possibly two elements to explaining why. One is that the patients for such products are mainly children, which makes prescribers more hesitant about using an experimental product since this is how many see Biosimilars with their unproven history of safety and efficacy. There is though also the problem of a lack of interchangeability mentioned earlier that has handicapped the market in Europe for all Biosimilars to some degree. Where products are not interchangeable, the pharmacist no longer has the option of substitution and has to dispense what is prescribed.

Data from IMS for the period up to March 2011 showed that Biosimilar market shares for HGH ranged from as low as 6% in Austria up to a maximum of 34% in Romania, although most other countries had shares below 20%. With EPO (Erythropoietin), the picture is more positive although some countries still lag behind – Italy had only 7% MS for Biosimilars and the UK, surprisingly, only 9%. Many other countries though had market shares in excess of 50% - Germany showed 65%, Greece 67% and Poland 62%.

Given the size of its market, Germany is the most significant and what seems to have happened here is that the government and Sick Funds effectively "genericised" EPO by setting quotas for Biosimilar use. There is an additional factor in Germany in that EPO is bought extensively by dialysis clinics, many of which are privately owned with an interest in buying lower cost medicines, thereby making them ideal customers for Biosimilar EPO.

No doubt, more recent figures for Biosimilar penetration in Europe will show further increased penetration as they become more widely accepted and as the pricing war comes to more closely resemble that fought out at the small molecule level.

In other parts of the world such as Latin America, many Biosimilars are bought on tender leading to what is in effect substitution as this year's tender winner is dispensed in place of last year's tender winner. There do not seem to have been any reports of widespread immunogenic reactions as a result of switching.

Does this mean that the standard of pharmacovigilance in Latin America is too poor to pick up such side effects? Or does it mean that Europe's regulators and prescribers have been too cautious on the topic of Biosimilar interchangeability and substitution?

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January 2012
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