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The other path for follow-ons

With follow-on biologics essentially dead in the water in the US, the decision of the world's largest generics manufacturer to invest in a platform for enhancing protein pharmacokinetics could pay dividends.

Evergreening is a practice familiar to many in the pharmaceutical industry. It involves the reformulation of a brand drug so that the manufacturer's patent monopoly and period of market exclusivity can be extended, effectively delaying generic competition. Earlier this year, Israeli generics drug manufacturer Teva made a move in the area of follow-on biologics that takes a leaf out of big pharma's evergreening book. Using albumin fusion technology acquired with the purchase of Human Genome Sciences spinout CoGenesys, Teva is making 'souped-up' versions of brand biologics with superior pharmacokinetics. Compared with the traditional generics strategy of simply copying biopharmaceuticals and undercutting brand price, these albumin fusions and other reformulation technologies not only have the potential to create superior products from incumbent molecules, but also neatly sidestep the legislative deadlock that has so far stranded traditional follow-on biologics.

That deadlock results from emerging regulatory positions that hinge on the process-to-process variability within biologics manufacturing. The European Medicines Agency biosimilars regulation already requires comparative clinical trials to demonstrate clinical equivalence to brand products. And Janet Woodcock, of the FDA's Center for Drug Evaluation and Research, is on the record as telling generics companies "you are not going to be able to show, nor are we going to be convinced, that two proteins are exactly the same; for proteins, it's the degree of similarity."

Thus, interchangeability of biopharmaceutical brands now looks more and more far fetched. Furthermore, would-be generics manufacturers must confront the prospect of long market-exclusivity periods for brand products that may emerge in new legislation. Last month, Duke University economist Henry Grabowski (*Nat. Rev. Drug Discov.* **7**, 479–488, 2008) suggested that the break-even time (and thus minimum period of data exclusivity) for an average biopharmaceutical product is between 12.9 and 16.2 years (depending on discount rates). If the legislation reflects those data, then over 12 years would be a long time for a manufacturer to wait until it can market its generic and recoup the development costs. Thus, a combination of economics and legislative restrictions appears to be steering the biologics industry in the direction of functionally improved compounds that aim to compete on performance rather than just price.

There are many protein-derivatizing technologies, each of which can be applied to a wide range of protein and peptide molecules. The one that Teva is using—the fusion of human albumin to the C or N terminus of biopharmaceuticals—illustrates the likely impact of the whole set. Albumin acts as a guardian for the bound protein, reducing renal clearance, increasing solubility/stability and extending half-life to about 2 weeks, all without compromising tertiary folding or therapeutic activity. The improved half-life potentially allows lower and less frequent dosing and better tolerability, making treatment cheaper and enhancing patient compliance and safety.

Novozymes, which owns the intellectual property that Teva licensed, claims the albumin technology has now been successfully applied to over 50 proteins. Just weeks ago, Dyax negotiated a license to develop enhanced versions of Kunitz domain proteins and antibody fragments for therapeutic and diagnostic applications (see p. 718). And in April, CSL Behring licensed the same technology to develop an extended-life version of coagulant factor VIIa. Albumin fusions appear to be a broad and adaptable platform for second-generation biologics—from small (30-mer) peptides to much larger antibody fragments (60–120 kDa).

Albumin-protein fusion is not the only turbo technology available to biologics developers, of course. At the Biotechnology Industry Organization annual meeting in San Diego this June, there was a buzz about chemical modifications (e.g., PEGylation derivatization with hydroxyethyl starch, altered glycosylation, albumin conjugation or encapsulation) or genetic modifications (fusions with albumin or elastin-like peptides or incorporation of unnatural amino acids) to supercharge proteins.

The bottom line, then, is that although there are a limited number of original protein drugs, there is a wide variety of ways of potentially improving their performance. In every case, of course, that improved performance has to be proved in the clinic. But as straight generic copies of biologics are likely to face the same clinical barriers to the market (plus brand exclusivity provisions), manufacturers have virtually no incentive to develop biologics without improved performance, especially if second-generation products can enter the market before patent expiration of the original brand.

Whether albumin fusion technology—or any other reformulation strategy—will bring enough companies onto the biopharmaceutical market to generate sufficient price competition and lower costs for health providers and patients is another matter. Economics research suggests at least four or five firms need to enter a market before discounting benefits are seen.

What is clear is that most existing makers of biopharmaceuticals aren't going to be leading the price-cutting charge. One need only look at the high prices of long-acting versions of epoetin alpha (Aranesp) and interferon α2b (Pegintron) produced by Amgen and Schering-Plough, respectively.

So the future of low-price, second-generation biologics probably lies elsewhere. Competition will not be between innovators and price-cutting copiers; it will be between financially robust innovators—companies that can afford to run the necessary clinical studies. Some brand manufacturers will likely act defensively by licensing-in or acquiring derivitization approaches (even if they don't intend to use most of them). Parenthetically, financial regulators might like to be on the lookout for such market-protective and monopolistic acquisitions.

In the meantime, larger generics companies, like Teva, and pharmaceutical companies now have the chance to seize the risk-reduced opportunity that derivatized biologics represent. It is they who have the wherewithal and resources to undertake the necessary R&D. And it is they who can create the kind of competition in biologics markets that could have arrived—some would say, ought to have arrived—with the original introduction of 'generic' biologics.