*'Supergenerics offer real product differentiation, patent protection, and branding opportunities for product manufacturers.'*

# editorial

**Stephen A. Charles**
Vice President of Business Development,
Nektar Therapeutics

**Stephen Alexander Charles, PhD is the Vice President of Business Development at Nektar Therapeutics' Division in Huntsville, AL. Prior to Nektar, he held senior R&D and commercial positions with several biotechnology companies including Amersham International plc, Biocompatibles International plc, Oxford GlycoSystems and PolyMASC Pharmaceuticals plc. Dr Charles has a PhD and a BSc in Biochemistry from the University of London.**

# SuperGenerics: a better alternative for biogenerics

Although the first biogeneric drug has yet to be approved in the USA or Europe, a potentially explosive industry is waiting to launch once the first wave of biopharmaceutical patents begin to expire. The prospect of biogenerics and its impact on biotech product sales looms large for the biotechnology industry. Eleven biotech drugs are slated to lose patent protection by 2006, which represents projected combined global sales in 2004 of USD$50 billion [1].

The biogenerics market is different in several ways from the traditional generic market for small molecule pharmaceuticals. By definition, a traditional generic drug is essentially the same as the original drug, incorporating the active pharmaceutical ingredient for which the patent has expired. It is typically approved through a simplified registration process and then sold under a common, rather than brand, name.

In a typical generics market scenario, a drug goes off patent and competitors rapidly penetrate the market within weeks. This results in a significant price decrease, the product becomes a commodity, and the original drug maker suffers a sharp loss of market share and revenues.

A biogeneric is essentially a biological equivalent of the original therapeutic that can be manufactured following patent expiration. Bringing a biogeneric drug to market has more barriers to entry than a traditional generic; however, the revenue potential for these drugs gives incentive for generic drug companies to overcome the challenges.

Unlike small molecules, there is no accelerated approval process in place for biogenerics and major regulatory agencies are yet undecided on the exact route of approval for these drugs. Currently, a full development program is required but generics manufacturers are fighting to change that. This regulatory battleground is set for 2005.

When selecting a drug as a candidate for a follow-on generic, traditional pharmaceutical and biopharmaceutical molecules share some basic criteria. For example, generics manufacturers typically target drugs with a large market size that can offer a high return on investment. They will also examine whether the branded product can be made less expensively

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as a generic because of a lower cost-of-goods and a simple, non-proprietary formulation system.

In the case of biogenerics, however, some special criteria apply. For example, manufacturers must determine the availability of active ingredient via a non-patent infringing route, a well characterized active ingredient with easy to match specifications, and determine the bioequivalence of the generic version, physio-chemical characterization, impurity profile, and glycosylation. All of these factors are critical in production of these drugs.

Because a full-fledged development program will be required to bring a biogeneric to market, why not bring a differentiated and better biologic product to market with little to no increase in development cost?

A supergeneric offers this differentiation because it changes the original biological product in formulation or method of delivery, and sometimes even efficacy. Supergenerics offer a higher-value alternative to biogenerics because these differentiated products are eligible for patent protection, three years of marketing exclusivity, and branding opportunities.

Consider erythropoietin (EPO), which is still under patent by Amgen under the brand name EPOGEN® (epoetin alfa), bringing Amgen USD$2.6 billion in revenue in 2004. More than 20 forms of biogeneric EPO are currently in development, the majority of which are in the pre-clinical phase.

These full-fledged EPO development programs will incur a development cost akin to the development of an entirely new biological drug. As a result it is likely that many products will enter the market around the same time, causing stiff price competition, which will likely result in disappointing return on investment for manufacturers.

On the other hand, take an example of a differentiated supergeneric, Roche's PEGASYS® (pegfilgrastim), a PEGylated form of interferon α-2a. In clinical trials of PEGASYS in patients with hepatitis C, three times as many patients showed undetectable levels of viral RNA when treated with PEGASYS, compared with those treated with unPEGylated interferon α-2a. [2,3] Moreover, the incidence of antibodies fell from 15% to 1.5% with PEGASYS compared to its unPEGylated counterpart, and antibodies that formed were largely non-neutralizing. Also significantly, patient compliance with therapy improved, as only one weekly injection of PEGASYS was required compared to three weekly injections for the unPEGylated interferon α-2a. Today, PEGASYS has become the market leader for interferon therapeutics for the treatment of hepatitis C.

As outlined in the preceding case study, PEGylation represents one strategy for creating supergeneric biopharmaceuticals. The conjugation of proteins with polyethylene glycol (PEG) is now a clinically-proven and approved technology for enhancing the therapeutic performance of this drug class. Six approved PEG products using technology from Nektar Therapeutics are marketed today and many more are currently in clinical trials. Benefits which can be achieved through the application of Advanced PEGylation technologies include extended circulation lifetime, improved biodistribution, decreased immunogenicity, increased solubility, decreased proteolytic degradation, and greater stability of the drug product on storage.

Another strategy for creating supergeneric biopharmaceuticals is to offer a more patient friendly mode of delivery to traditional injections. For example, pulmonary drug delivery has long held appeal, not only for disorders directly affecting the lung, but as a non-invasive alternative to injections for systemic conditions that cannot be treated using oral medications (i.e. those that require macromolecule drug therapies).

Recent advances in the technologies used to manufacture drug powders for inhalation – particularly particle engineering and formulation methods to control particle size, morphology, consistency, dispersibility and chemical stability – have created exciting opportunities to expand the applications for pulmonary delivery to many therapeutic molecules, including proteins and peptides.

Delivery of macromolecules to the deep lung for systemic disease has certain biological advantages. The alveolar epithelium that lines the lungs naturally absorbs proteins and peptides without enhancers, and offers an enormous surface area for absorption at low local drug concentration and with rapid onset of action.

Inhaled versions of macromolecule therapeutics in development have shown considerable promise. Pulmonary insulin, in particular, is now in the late stages of human clinical testing with the most advanced version, Exubera® (inhaled insulin), filed for marketing approval in Europe by Pfizer and Sanofi-Aventis. Whereas this is more a case of a supergeneric version of a previous generic drug, rather than an off-patent branded drug, clinical data for Exubera® have indicated its ability to provide glycemic control as well as insulin injections [4–8] and better glycemic control than combinations of oral diabetic agents. Additionally, preference studies with diabetic patients have underscored their desire for such an alternative to injections. [9–11] So, not only does the product demonstrate better performance and potential for better compliance, it also offers its manufacturers branding opportunities and better return on investment.

In the complex and high-risk field of biotech drug development, simply developing a generic copy of an existing drug is not sufficient to be competitive. Further, the high risk, long development time and higher costs associated with bringing a biological drug to market necessitate a strategic approach to biogeneric drug manufacturing.

Biotechnology companies need to examine their alternatives to long-term regulatory processes to address the follow-on biologics market. Supergenerics offer real product differentiation, patent protection, and branding opportunities for product manufacturers. This new product category addresses an important market need to expand the availability of important therapies and reduce time to market.

## References


1 Class, S. (2004) *Biogenerics: waiting for the green light,* IMS Health
2 Heathcote, E.J. *et al.* (2000) Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N. Engl. J. Med.* 342, 1673–1680
3 Zeuzem, S. *et al.* (2000) Peginterferon alfa-2a in patients with chronic hepatitis C. *N. Engl. J. Med.* 343, 166–1672
4 Hollander P. Efficacy & Safety of Inhaled Insulin (Exubera®) compared to sc insulin therapy in patients with type 2 diabetes: results of a 6-month, randomized, comparative trial, for the Exubera phase III study group. Late-Breaking Poster for President's Poster Session, American Diabetes Association, 61st Scientific Sessions, Friday, June 22-Tuesday, June 26, 2001.
5 Cefalu, W.T. *et al.* (2001) Inhaled Human Insulin Treatment in Patients with Type 2 Diabetes Mellitus. *Annals of Internal Medicine* (Vol. 134) pp. 203–207
6 Cefalu, W.T. *et al.* (2000) Sustained Efficacy and Pulmonary Safety of Inhaled Insulin During 2-years of Outpatient Therapy. *Diabetes: Abstract Book*, 60th Scientific Sessions, Friday, June 9 – Tuesday, June 13, 2000, p. A101.
7 Skyler, J.S. *et al.* (2001) Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomized proof-of-concept study. *Lancet* 357, 331–335
8 Rosenstock, J. (2002) for the Exubera® Phase III study Group. Mealtime Rapid-Acting Inhaled Insulin (Exubera®) Improves Glycemic Control in Patients with Type 2 Diabetes Failing combination Oral Agents: A 3-month, Randomized, Comparative Trial. *Diabetes: Abstract Book, 62nd Scientific Sessions (American Diabetes Association)*, Friday, June 14 – Tuesday, June 18 2001, A132
9 Su, M. *et al.* (2002) The Relationship between Regimen Burden and Psychological Well Being in Persons with Type I Diabetes: Inhaled vs. Injectable Insulin. *Diabetes: Abstract Book, 62nd Scientific Sessions (American Diabetes Association)*, Friday, June 14-Tuesday, June 18, 2002. p. A448.
10 Cappeleri, J.C. *et al.* (2001) Relationship Between Improved Patient Satisfaction and Improved Glycemic Control in Patients with Type 1 and Type 2 Diabetes Mellitus Treated with Inhaled Insulin: Pooled Results from Two Multicenter Randomized Controlled Trials. *Diabetes: Abstract Book, 61st Scientific Sessions, Friday, June 22-Tuesday, June 26, 2001*. p. A108.
11 Simonson, D.C. *et al.* (2001) Treatment satisfaction and preferences in Type 2 Diabetes: A randomized trial of oral agents vs. inhaled insulin. 3-month study included: patients on oral agents only; patients on both inhaled and oral agents; patients on inhaled insulin only (monotherapy). *Diabetes: Abstract Book, 61st Scientific Sessions, Friday, June 22 – Tuesday, June 26, 2001*. p. A131.



***Stephen A. Charles***
*Nektar AL,*
*490 Discovery Drive,*
*Huntsville, AL 35806, USA*
*sacharles@al.nectar.com*