Perspective

The Promise of Biogenerics: Hope and Hype

By Mukesh Kumar, PhD

The year 2007 can be seen as the year when generic biologics came to the forefront of discussions in regulatory, scientific and business circles. Three bills were introduced in the US Congress to create an abbreviated approval pathway for biologics, like the one for conventional drugs.[1] In March, the House Committee on Oversight and Government Reform held a hearing to discuss the need such a pathway and explore ways to create generic biotech drugs.[2] Numerous reports—from professional, consumer and academic groups—were published in favor of and in opposition to the quick approval of regulations allowing generic biologics. One of the major reasons for this hoopla was that several important FDA regulations (including *PDUFA* and *MDUFMA*) were coming up for reauthorization in 2007 and the major stakeholders promoting biogenerics saw an opportunity to insert provisions for them. However, after prolonged and sometimes contentious discussions, biogenerics were omitted from the *FDA Amendments Act* of 2007, which was signed into law on 27 September. One wonders if biogenerics were excluded as the result of political pressure from influential groups or an extremely cautious approach on the part of the legislators.

Three major factors influence the future of true biological generics. First, due to the complex nature of biologics, a strong scientific case can be made that it is practically impossible to create an exact copy of a biologic drug. FDA has stated many times that the "process is the product," and minor differences in manufacturing could lead to major changes in the clinical outcomes of a generic product.[3] Both FDA and EMEA have resisted the term "biogenerics," preferring the terms "biosimilar" and "follow-on biologics" to emphasize that while products might be "similar," they are not necessarily "bioequivalent."[4,5] It has also been stressed that to be truly substitutable, a product would require extensive and costly preclinical testing and clinical trials.

Second, there are no regulatory shortcuts, like the ANDA, for biogeneric approval. FDA has approved some follow-on proteins on a case-by-case basis without requiring extensive preclinical and clinical testing. Nevertheless, the amount of testing required by FDA for these follow-on proteins was much higher than that for generic drugs. More importantly, all were approved in the manner of innovator products, not as substitutable generic versions. The oft-cited EMEA "biosimilar" guidance is unequivocal in stating the need for much more clinical and preclinical data to prove safety and comparability than is expected for generic chemical drugs. While the supporters of biogenerics would like to lift parts of the EMEA process to justify similar regulation in the US, the EMEA process is not an ANDA-style shortcut for biologics and does not define substitutability of biosimilars for innovator products.

Third, unlike a chemical drug, a biologic typically is covered by multiple patents, not only on the product, but also on many of the basic research tools used to develop it. In addition, manufacturing might use proprietary processes covered by trade secrets. While the patents have a finite life, trade secrets can remain protected forever. FDA may, however, refer to non-public proprietary information to compare a similar product's safety and efficacy.[6] Still, extensive use of proprietary technologies makes it much more difficult to create true copies of biologics.

Are We Ready for Biogenerics?

Despite the obvious hurdles to biogenerics, there is an enormous push in their favor. Generic manufacturers want access to the potentially huge market for these products, while consumer groups and legislators see the promise of significant cost reduction.[7] However, FDA's major concern is safety.[3,4] The bioequivalence of biogenerics must be defined and validated. Plato said, "Necessity is the mother of invention." The technology to evaluate similar biologic products without extensive human testing will develop with time and, for at least a few biologics, such technology already exists. But there is no one-size-fits-all approach and probably never will be.

While no one denies that biogenerics will lead to cost savings, there is disagreement about the extent thereof. One projection of potential cost savings is about $70 billion over 10 years;[8] however, other estimates project modest savings of less than $4 billion over 10 years.[9,10] The lower projected numbers dampen the spirit of consumer groups expecting huge savings. The development of each biogeneric product will be a lengthy, complex process, and is projected to cost about $200 million, compared to

approximately $30 million for a traditional generic drug. This leads to the assumption that only a few generic firms will be able to afford the required investments, and only products with a significant market will be developed. Fewer entrants in the biogeneric field could mean a lack of the robust competition required for cost reduction. Still, for treatments that cost thousands of dollars a year, a saving of 10% to 20% might be enough to justify development. Consumer acceptance of biogenerics will be critical to determining market size. Since it may not be possible in the near future to have truly substitutable generic versions of biologics, physicians will need to prescribe specific biosimilars. Prescribing a biosimilar product with some unknowns rather than an established innovator product could raise some ethical issues. However, once biosimilars have established credibility and are widely accepted, more players will be willing to risk investment in this field, resulting in further cost reductions.

Generic biologics hold great promise. It is inevitable that regulations for biosimilars or follow-on biologics will be implemented in the near future; the "hype" for these products is simply too high for politicians to ignore. But, it would be prudent for the policymakers to tread carefully in order to truly harness the "hope" of safe, efficacious and cost-effective products.

REFERENCES

1. *Access to Life-Saving Medicine Act*; H.R. 1038 & S. 623, 110th Cong. (2007). *Affordable Biologics for Consumers Act*; S. 1505, 110th Cong. (2007). *Patient Protection and Innovative Biologic Medicines Act* of 2007; H.R. 1956, 110th Cong. (2007).
2. March 2007, the House Committee on Oversight and Government Reform (chaired by Representative Henry Waxman (D-CA): "Hearing on Safe and Affordable Biotech Drugs – The Need for a Generic Pathway." *http://oversight.house.gov/story.asp?ID=1223*
3. Janet Woodcock, et al. (2007). "The FDA's assessment of follow-on protein products: A historical perspective." *Nature Reviews: Drug Discovery.* Vol. 6, p 437-442.
4. *www.ftc.gov/speeches/harbour/070614genbio.pdf*
5. *EMEA Guidelines for Similar Biological Medical Products.* CHMP/437/04, 30 October 2005.
6. Yoo JC. "Taking Issue in the Approval of Generic Biologics." 60 *FOOD & DRUG L.J.* 33 (2005)
7. Conko G. "Healthy Competition: The Case for Generic and Follow-on Biologics." *www.cei.org/pdf/5933.pdf*
8. Miller S & Hounts J. "Potential Savings of Biogenerics in the United States." *Express Scripts.* February 2007.
9. *www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf*
10. *http://faculty.fuqua.duke.edu/health_sector_management/hsac/files/oct%2020_26_2006/Biogenerics_Ridley%20et%20al.pdf*

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