

Biosimilars: Challenges and Promises CABS Workshop on Biosimilar Therapeutics

Jared Higbee and Hua Tu

A CABS-sponsored workshop, “Biosimilars: Challenges and Promises,” was held on September 26, 2009 in the conference room of Orrick, Herrington & Sutcliffe, LLP in Menlo Park, California. This 4-hour workshop was organized and moderated by Yingfei Wei, CSO of 3SBio, and was attended by over 100 CABS members and guests. There were five talks in total, covering a range of topics including production strategies, clinical development, CMC and regulatory requirements, biosimilar legislation, protection of intellectual property, and investors’ perspectives.

The timing of this workshop coincides well with the current environment of the biopharmaceutical drug industry. Biologics, also known as large-molecules, differ from the more common small-molecule drugs in that they generally have a greater degree of molecular complexity, and are highly sensitive to changes in manufacturing processes. Currently, large-molecules account for nearly 20% of marketed pharmaceuticals with projections expected to reach 30% by the year 2014. Based on the number of Biologic License Applications (BLA) that are being filed, biologics are expected to experience the most growth out of all human therapeutics within the coming years, especially in the domain of monoclonal antibodies. At the same time, several of the biggest name biologics on the market today (recombinant insulin, human growth hormone, erythropoietin, GCSF, and Enbrel®) will face patent expirations in the US over the next few years, creating potentially a 40 billion dollar opportunity for biosimilars. Also known as Follow-On Biologics (FOB) or copycat drugs, biosimilars are officially approved versions of existing large-molecule therapeutics that have come off patent. A major distinction between generic small molecules and biosimilars is that follow-on developers do not have access to the innovator’s molecular clone, master cell bank, or knowledge of the exact fermentation and purification processes. Therefore, the challenge of developing biosimilars is to thoroughly demonstrate that a follow-on product is indeed similar, in terms of safety and efficacy, to a currently approved biologic. Biosimilars are already on the market in Europe where patent terms are shorter and the regulatory framework is better defined. In the US, however, the biosimilar legislation is still a work-in-progress, and how America’s pharmaceutical industry will tackle the challenges of biosimilar development is of great interest and significance.

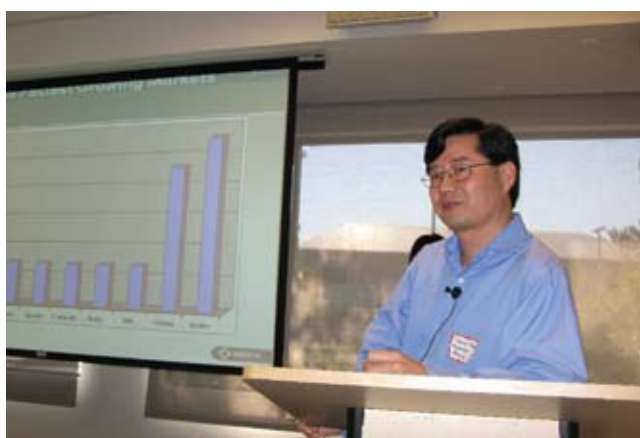


Figure 1. David Shen

Dr. Wenyan “David” Shen, Executive Director and Head of Biologics Basic Research at GlycoFi, Merck & Co., Inc., gave the keynote speech. Merck announced its plans of entering the biosimilar market in December of 2008, and Dr. Shen is a key driver in this campaign. He elaborated on that decision by stating that the pursuit of biosimilars will concurrently bolster Merck’s capabilities for developing innovative large-molecule drugs, and considering the magnitude of opportunity in follow-on products, differentiation by a lower cost is highly desirable. However, the biggest obstacle in biosimilar development is that of manufacturability and controlling the heterogeneity and impurity profiles of the final product. Dr. Shen emphasized that because large-molecules are made in living systems, even very slight perturbations in the manufacturing process can have dramatic effects in the quality of the final product. Differences in the post-translational modification (i.e. glycosylation) of proteins can greatly influence factors such as biostability, FcR-mediated effector function, excretion, and immunogenicity. Such was the case with Raptiva®,

an anti-CD11a monoclonal antibody developed through collaboration between XOMA and Genentech. Although the same manufacturing protocol was followed, the Raptiva produced at XOMA had different pharmacokinetic properties than Genentech's product. In this case, improvement of pharmacokinetic behavior by Genentech did not translate into an improvement in efficacy for Psoriasis. Another challenge associated with the manufacturing of biologics is that of process scalability as exemplified by the efforts of Genzyme Corporation to increase production of recombinant alglucosidase alpha (Myozyme[®]) from the 160 L to 2000 L scale. Increasing the production scale caused slight changes in the glycosylation of Myozyme, which provoked the FDA to require a separate BLA filing for the 2000 L product.

Dr. Bao-Lu Chen, Director of Manufacturing and Process Development at Sangamo BioSciences, provided insight on the processes required to bring large-molecule therapeutics to the market. He stressed that even if a biosimilar is equally as efficacious when compared to the innovator's product, slight changes in the manufacturing process can greatly alter the safety profile as a result of exacerbated immune responses; and although we have the analytical capacity to detect slight differences in micro-heterogeneity between a biosimilar and its reference molecule, the burden of proof ultimately lies within the clinical setting. Chen did, however, provide a more encouraging case of biosimilar production by citing Biogen's development of Avonex[®], a less complex molecule than Myozyme. The original clinical molecule, BG9015, was developed through a 50/50 joint venture with Rentschler Biotechnology, and Avonex was generated at a different site using substantially different processes including a unique CHO cell line as the expression host. Despite these substantial changes to the manufacturing process, Biogen was able to rely on the results of a BG9015 clinical study for the FDA's approval of Avonex after demonstrating therapeutic equivalence between the two molecules. The case of Avonex is significant in shaping the regulatory landscape for biosimilars because it demonstrates that clinical efficacy and safety can be manageable for products derived from different processes, and even different cell lines.

Dr. Peony Yu, a clinical development executive at Fibrogen, delineated the clinical development aspects of bringing biosimilars to the market. An advantage for follow-on biologics is that the standard phase II study requirement for innovative compounds can be circumvented by demonstrating comparable safety and efficacy between a biosimilar and its reference compound, thus saving a considerable amount of time and money through abbreviation of the clinical process. However, the cost-saving benefits are not the only attractive qualities of biosimilars. By merely demonstrating similar safety and efficacy in the clinic for a particular indication, the biosimilar can garner all of the currently approved label indications of the innovative product. Dr. Yu used the approval of Sandoz's Omnitrope[®] for the treatment of hormone deficiency in both adult and pediatric populations as an example. Although the clinical evaluation of Omnitrope was conducted in children, Sandoz was able to gain an additional indication for treatment of adults by citing original data published for



Figure 2. *Bao-Lu Chen*



Figure 3. *Peony Yu*

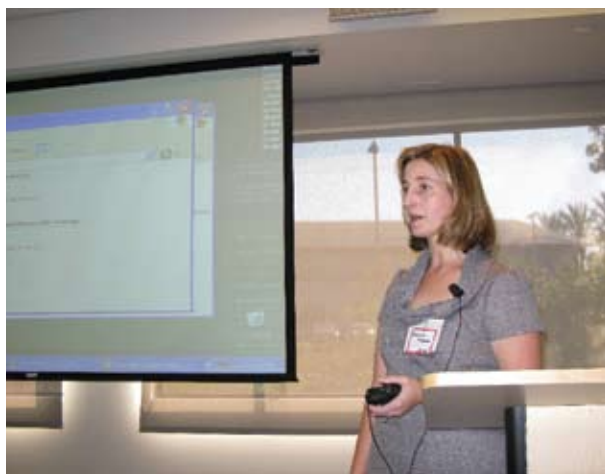


Figure 4. *Fishman*

the reference compound, Genotropin[®]. In essence, by proving therapeutic equivalence, a biosimilar product can utilize data from the innovator to gain access to all of the approved indications without actually conducting such trials. Thus for many pharmaceutical companies, this makes yet another good reason for initiating a biosimilar development campaign.

Deborah Fishman, an intellectual property attorney and partner at Orrick, Herrington & Sutcliffe, LLP, gave a talk titled “Biosimilar Legislation and its Impact on Protecting and Enforcing IP Rights”. Ms. Fishman focused on the regulatory structures for biosimilars, and reviewed the EMEA framework for “similar biological medicinal products”. She further compared the three proposed biosimilar legislations from the Waxman, Eshoo/Inlee, and Hatch/Enzi amendments, which are currently being debated in Washington. The key issue is establishing a term for data exclusivity, which in the current proposals ranges from 5 to

12 years, with the Obama Administration currently favoring a 7 year term. Because patent term extensions generally run short because of long clinical development campaigns, data exclusivity is crucial since it is the one clause that offers protection for innovator drugs. Ms. Fishman summarized that the proposed biosimilar legislation has not yet addressed intellectual property rights. If any bill becomes law without adding a provision to protect intellectual property, an amendment may be necessary, and some of the issues may have to be resolved later in the judicial system.

Dr. Marietta Wu, from Burrill & Company, spoke from the investor’s perspective in her talk titled “Biosimilar: On the Brink of Accelerated Growth”. Dr. Wu’s talk was armed with graphics and data. The market for large-molecule drugs is growing significantly faster than the market for small-molecule drugs, and the biosimilar market is expected to gain momentum from 2010 onward due to patent expiries. However, biosimilar economics is different from the economics of small molecule generics. Clinical trials for biosimilars are required, and the associated costs and risks are significantly higher. It may cost more than 100 million dollars to bring a biosimilar to market, staggeringly higher than generics, which require no clinical trials. Dr. Wu further highlighted the challenges to produce carbon copies of biologic drugs along every step of the production process, and emphasized that the development timelines for biosimilars are comparable to that of a new biologic entity, only the risk of failure is smaller. Because of the higher barriers to enter the biosimilar market, the number of players will be fewer. Currently, the biosimilar landscape is driven by top generic producers such as Sandoz (Novartis), Teva (formed biosimilar joint venture with Lonza), and Dr. Reddy’s. Investment opportunities are concentrated in developing countries and commercialization specialists for which the capital requirements are low. Although the time to commercialization is short, the competition is fierce.

In summary, the development of the biosimilar market may evolve to be a lucrative opportunity for many in the pharmaceutical industry and investors alike, and at the same time offer the promise of bringing cost-effective alternatives to patients who desperately need affordable treatments. Although the technology is currently in place to make safe and effective follow-on biologic medicines, it is challenging to establish a well-defined regulatory structure that can simultaneously foster biosimilar development and preserve an incentive for innovators to create novel therapeutics.

Contact Authors: Dr. Jared Higbee, Amgen, Inc. E-mail: jmhigbee@amgen.com; Dr. Hua Tu, LakePharma, Inc. E-mail hua.tu@lakepharma.com