REPRINT FROM

GEN Genetic Engineering & Biotechnology News

Biotechnology from bench to business

Volume 31, Number 11 **June 1, 2011**

OMICS | Drug Discovery | Clinical Research & Diagnostics | Bioprocessing | Biobusiness

Legal Affairs

Making Follow-On Biologics a Reality

Analytical Chemistry Methods Have a Multifaceted Role in This Complex Process

Graham B. Jones and Janis K. Fraser

Graham B. Jones (gr.jones@neu.edu) is head of the department of chemistry & chemical biology and The Barnett Institute of Chemical & Biological Analysis at Northeastern University. Janis K. Fraser (fraser@fr.com) is a principal at the law firm of Fish & Richardson.

In view of the success of generic small molecule pharmaceuticals in competing with their branded equivalents, it's not surprising that many parties want to bring lower-cost copies of biopharmaceuticals to market as well. A significant impediment has been the perception that the complexity of biopharmaceutical agents (biologics) makes it impossible to ensure that a purported copy, or follow-on biologic (FOB), is really identical to the original.

After years of debate about the very concept of FOBs, the federal government in March 2010 took a huge step toward making FOBs a reality by enacting the Biologics Price Competition and Innovation Act. The act created the long-awaited statutory framework for U.S. FDA evaluation and approval of FOBs.

Given that 2010 worldwide sales of biologics approached the $100 billion mark and several of these agents are due to come off patent in the next five years, the act is likely to have profound consequences in the biotechnology and healthcare sectors. The act is intended to encourage innovation and to promote price competition by being responsive to the needs of both the biologic license application (BLA) holder who originally developed and marketed the biologic (the reference product) and the FOB applicant who wishes to compete by offering a similar product at a lower price, without having to do full-scale clinical trials.

The act outlines two pathways whereby FOB applicants can seek approval: 1) as biosimilar to the reference product, where the FOB is deemed highly similar to the reference product; and 2) as interchangeable with the reference product, where the FOB is deemed essentially identical. Clearly, the standards for interchangeable will be especially stringent, but in both categories it is expected that considerable scrutiny will be placed on criteria used to demonstrate equivalence of the FOB to the sponsor/reference product.

Biosimilarity and Bioequivalence

In November 2010, FDA held a public hearing to solicit input on 1) scientific and technical factors it should consider in determining whether the biological product is highly similar to the reference product; 2) scientific and technical factors it should consider in determining what studies are appropriate for assessing the nature and impact of actual or potential structural differences between the proposed biosimilar product and the reference product; 3) the range of structural differences between a proposed biosimilar product and the reference product consistent with the standard "highly similar;" and 4) criteria FDA should apply to determine whether animal and/or clinical studies are unnecessary for submission of a FOB application.

Of significance to protein-based FOBs in particular, FDA had earlier identified three properties of therapeutic proteins that, in its opinion, cannot be sufficiently measured at this time, but that are deemed important for understanding the behavior of protein drugs: post-translational modifications, "higher-order" structures, and protein aggregates. Methods used to investigate these properties are likely to be crucial for the FOB approval process for protein-based FOBs, which are expected to constitute a significant component of the marketplace.

Protein-Characterization Methods

Post-translational modifications of proteins encompass a wide variety of modifications, including glycosylation, oxidation, phosphorylation, sulphation, lipidation, disulphide bond formation and deamidation. Mass spectrometry (MS) has become the tool of choice for detecting and investigating these modifications.

In some cases, nuclear magnetic resonance spectroscopy (NMR) can also be useful. Indeed, it was NMR that identified the recently publicized issue of heparin contaminated with O-linked glycans.

The so-called higher-order structure of a protein gives it its unique 3-D shape and thus contributes to its functions. Subtle differences in such higher-order structures might explain observed biological/immunological differences between otherwise identical proteins and also serve as a basis for comparison of reference products with FOBs.

Myriad classical biophysical techniques are used to characterize higher-order structures, including circular dichroism, fluorescence, differential scanning calorimetry, isothermal calorimetry, analytical ultracentrifugation, and size-exclusion chromatography. Detecting subtle changes requires use of additional techniques such as NMR, x-ray crystallography, and MS.

Formation of undesirable protein aggregates represents a substantial problem for biopharmaceuticals. Aggregates can display adverse toxicological and immunological profiles, in addition to having an obvious detrimental impact on dosage. Characterizing aggregates is a complex undertaking. Among the numerous methods employed are size-exclusion chromatography, analytical ultracentrifugation, and asymmetric flow field flow fractionation. Detection of sub-visible particles present at very low concentration requires techniques such as dynamic or static light scattering.

Sophisticated analytical protein-characterization methods will likely have an impact, not only in establishing the similarity of a FOB to its reference product, but also in accounting for potential adverse clinical events. For example, a number of FOB versions of a human erythropoietin reference product (Eprex®) have been approved by the European Medicines Agency (EMA), and while these versions were deemed by EMA to be comparable in quality, safety, and efficacy to Eprex, clear differences in structure have been documented by analytical methods.

If any of these erythropoietin FOBs is, in the future, associated with adverse clinical events, these structural differences—and the fact that they were known in advance—may well play a role in potential litigation related to the adverse events. This, in turn, may influence similarity standards applied to FOBs by FDA and other regulatory agencies.

Patent Aspects

While the scientific and clinical underpinnings of the act are undergoing scrutiny, no less significant are the act's provisions regarding patent and data exclusivity. The act gives BLA holders 12 years of marketing exclusivity, but a FOB applicant can file its application at the FDA to start the process after just four years.

The act lays out a byzantine process in which the FOB applicant provides the BLA holder with access to confidential information regarding the FOB application for the purpose of assessing potential patent infringement, and then the parties go back and forth trading their views regarding the BLA holder's patents. The process culminates in lists of patent claims that are to be asserted by the BLA holder against the FOB applicant in two waves of patent litigation outlined in the act.

In the patent context, characterizing protein structure by analytical chemistry methods will sometimes be essential to determine whether a FOB infringes a patent claim or is structurally distinct from what is claimed. These methods might also be occasionally employed by a BLA holder who seeks to develop a new, improved version of its existing product to replace the original product in the marketplace prior to loss of market share to FOBs.

To obtain new patent protection for such an improved version, it may be useful to demonstrate just how it is structurally distinct from the original product. And regardless of patent issues, the act grants a new 12-year period of exclusivity for the BLA holder's improved product if the improved product is shown to have a biological structure different from the original product (provided that the new structure results in a change in safety, potency, or purity of the product).

With biosimilars due to become a reality soon, use of analytical chemistry methods to characterize proteins will take on ever-increasing importance. GEN