TECHNOLOGY & BUSINESS LAW ADVISORS, LLC

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Winter 2010-2011

The United States Patient Protection and Affordable Care Act of 2010: How Advances in Bioanalytics Might Cloud FDA Approval of Follow-On Biologics

On March 23, 2010, the United States Patient Protection and Affordable Care Act (PPACA) was signed into law establishing an abbreviated Food and Drug Administration (FDA) market approval pathway for follow-on versions of innovative protein drugs. Under the new pathway, applicants are required to submit pertinent analytical data demonstrating biosimilarity to the reference drug.[1] These follow-on biologics, if approved, are products shown to be biologically equivalent to a licensed reference biological product (e.g., an FDA approved drug already on the market) and are collectively referred to as biogenerics, follow-on biologics or biosimilars.[2] Title VII of the PPACA is similar in purpose to the Drug Price Competition and Patent Term Restoration Act of 1984 (i.e., the Hatch-Waxman Act [3]) in that both seek to improve public access to less expensive bioequivalent pharmaceuticals while maintaining the financial incentive for innovator companies to discover, develop and market new drugs.

One of the more highly contentious (and currently unresolved) issues revolves around how FDA will determine whether an approved follow-on biologic is "interchangeable" with the reference drug or merely "biosimilar" to it.[4, 5] This distinction is significant for at least two reasons. First, follow-on applicants who receive interchangeable status for their drug will be able to delay subsequent approval only of other interchangeable biologics for at least a one-year period.[6] Second, interchangeable biologics will be eligible for automatic drug substitution against the branded innovator biologic.[7] An important caveat is that an interchangeable biologic cannot delay the market entry of (i) any approved biosimilar drug having the same reference product as the interchangeable or (ii) any other related biologic drug—whether clinically interchangeable or biosimilar—alternatively approved under the traditional BLA pathway.[8]

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[1] *See* 42 U.S.C. §262(k)(2)(A). The nature and extent of supportive data is uncertain.

[2] Use of the term "biogeneric" has fallen out of favor in discussions regarding follow-on biological drugs as it may imply an inaccurate comparison to freely substitutable generic small molecule drugs. For clarity, the term "follow-on biologic" will refer to the broader class of biologic drugs that include both "biosimilar" and "interchangeable" biologics.

[3] *See* 21 U.S.C. §355(j).

[4] The term "biosimilar" is reserved for the subclass of follow-on biologics that are merely similar to, and thus distinct from, the reference biologic. "Biosimilar" follow-on biologics are not automatically substitutable and will require a prescription from a health care provider. The term "interchangeable" is reserved for the subclass of follow-on biologic that is essentially identical to (yet chemically distinct from) the reference biologic. "Interchangeable" follow-on biologics may be freely substituted without the intervention of a physician.

[5] A public hearing was held on November 2-3, 2010 at FDA to hear input from stakeholders regarding scientific criteria for determining biosimilar or interchangeable status.

[6] *See* 42 U.S.C. §262(k)(6) for details.

[7] *See* 42 U.S.C. §262(i)(3) for details.

[8] For clarity, a biologic drug sponsor has the option of gaining FDA approval via a full Biologics License Application (BLA) or via the abbreviated BLA (aBLA) pathway. The latter pathway carries some restrictions on what corporate entities are ineligible for market exclusivity. *See* 42 U.S.C. §262(k)(7)(C)(ii). *See also* "The United

Follow-on biologic applicants are statutorily required to submit bioanalytical studies supporting a claim of biosimilarity to the reference product.[9, 10] Compared to full clinical trials, analytic studies are theoretically a less-expensive way to support a claim of biosimilarity to a reference innovator drug. Bioanalytic studies will likely play an increasing role in the follow-on biologic sector by providing affordable cumulative data points for determining what is biosimilar and/or interchangeable to a reference biologic. Indeed, advanced bioanalytical methodologies were instrumental in the recent approval of an interchangeable version of a complex pseudo-biologic polysaccharide anticoagulant.[11, 12]

Finally, with the enactment of the PPACA, the mere existence of a formal FDA approval process for follow-on biologics will likely spur the development of next-generation bioanalytics. Tellingly, FDA has recently stated that advances in the following three areas of protein analytics would be beneficial to biologic drug development: (i) protein aggregation, (ii) protein post-translational modifications and (iii) three-dimensional protein structural analysis.[13]

The Harder You Look, The More You Will Find

Exemplary pharmaceutical and biopharmaceutical analytic methods include the following: x-ray crystallography, chromatography, protein sequencing, carbohydrate analysis (e.g., Eastern blotting), aggregation analysis via ion mobility spectrometry (IMS), enzyme-linked immunosorbent assay (ELISA), ligand binding assay (LBA), immunogenicity assays, cell-based assays, posttranslational modification analysis, mass spectroscopy (MS), hydrogen-deuterium exchange mass spectroscopy (HXMS), electron transfer dissociation MS (ETD-MS), collision induced dissociation (CID), nuclear magnetic resonance (NMR), flow NMR, micro-coil NMR, X-ray powder diffraction (XRPD), thermogravimetric analysis (TGA), gel electrophoresis, field flow fractionation (FFF and AF4), chromatography (HPLC and RPC), displacement chromatography, differential scanning calorimetry (DSC), Western blotting, bioassay, immunoassays, microcalorimetry, fluorescence spectroscopy, capillary isoelectric focusing (cIEF), UV/visible spectroscopy, dynamic light scattering (DLS, QELS, PCS), multiple angle light scattering (MALS), circular dichroism (CD), isotope-coded protein labeling (ICPL), infrared (IR) spectroscopy and Raman spectroscopy.[14]

States Patient Protection and Affordable Care Act of 2010: Clarifying "Exclusivity", "Evergreening" and "Related Entities" Terminology", Technology & Business Law Advisors, Fall 2010.

[9] *See* 42 U.S.C. §262(k)(2)(A)(i)(I)(aa). Notably, FDA reserves the right to waive the requirement of certain studies (e.g., analytic, clinical, animal) on a case-by-case basis. *See* 42 U.S.C. §262(k)(2)(A)(ii).

[10] Bioanalytics are also required of innovative biologic drug applications submitted under the BLA pathway.

[11] Momenta Pharmaceuticals Inc. arguably played such a role in FDA approval of a generic version of the branded polysaccharide drug Lovenox™ - albeit via the §505(j) "ANDA" pathway of the Federal Food, Drug and Cosmetic Act (FDCA). *See* "United States FDA Approval Of Generic Lovenox™: A First Glimpse At Follow-On Biologic Sameness", Technology & Business Law Advisors, Summer 2010.

[12] On a related note, both Momenta Pharmaceuticals and Peptimmune Inc. – a bioanalytic company specializing in peptide therapeutics - are developing §505(j) generic versions of Teva Pharmaceutical's branded multiple sclerosis peptide drug Copaxone™.

[13] Results from these studies - applicable to both innovative and follow-on biologics - will shed light on protein immunogenicity, stability, activity and potency. *See* Statement Of Steven Kozlowski, M.D., Director, Office of Biotechnology Products, Office of Pharmaceutical Science, Center for Drug Evaluation and Research, Food and Drug Administration, Department of Health and Human Services. Subcommittee on Technology and Innovation Committee on Science and Technology, U.S. House of Representatives, September 24, 2009.

[14] Currently, not all are optimal for protein-based drug analysis.

Initially, it may appear that improvements in bioanalytic capacity will be an unrestricted windfall for follow-on biologic drug sponsors. After all, the greater the number of detectable similarities between the reference biologic and the follow-on drug product, the more persuasive the follow-on biologic application will be. However, will it cut both ways? Will advances in bioanalytic technology simply reveal comparatively more differences than similarities and completely eliminate the possibility of any follow-on biologic gaining interchangeability status? Will such technological strides unintentionally make biosimilarity an increasingly difficult (and expensive) prospect? Differences can always be found if you look hard and long enough, particularly for complex protein drugs.

Bioanalytics: The Premature Death of Interchangeables

Patient safety is paramount at FDA. All innovative biologic drugs approved under the BLA pathway must have first amassed extensive analytical, preclinical and clinical trial data in addition to continual post-approval safety monitoring. Seizing an opportunity to distinguish their biological products, astute innovative drug sponsors[15] (and even a few follow-on/"biobetter" manufacturers[16]) overanalyze biologic drugs with the goal of establishing a de facto insurmountable equivalence bar for competing follow-on biologic applicants.[17] Follow-on biologic applicants should consider whether the ever-expanding sea of bioanalytical data will simply give FDA another scientific rationale to deny approval of their application.[18]

Innovator sponsors would be wise to invest in next-generation bioanalytics as a means to increase biologic drug "granularity" and refute claims of bioequivalence. Bioanalytic data could also serve a useful purpose in obtaining strong patent rights—serving to distinguish the drug product from prior art, argue against obviousness and/or satisfy enablement and written description requirements.[19] Greater reliance on manufacturing trade secrets will be an effective mechanism to conceal important analytical differences in follow-on drugs without tipping off the competition.

Follow-on applicants should always consider alternatively filing a traditional BLA to avoid having to meet or exceed impossibly high equivalency standards. Ultimately, FDA approval of follow-on biologics will likely require some form of pre-approval or post-approval clinical trial to support an ever-increasing supply of bioanalytic data—a requirement the PPACA was designed to minimize in the first place.

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[15] *See* Teva Pharmaceutical Citizen Petitions FDA-2009-P-0555 and FDA-2008-P-0529.

[16] *See* Peptimmune, Inc. Citizen Petition FDA-2010-P-0531 requesting FDA to reject any §505(b)(2) or §505(j) applications for "purported generic versions" of Teva Pharmaceutical's Copaxone™ (glatiramer acetate).

[17] Paradoxically, when supported either by (i) voluminous analytical data or (ii) a complete lack of analytical data due to technological limitations, sponsors often claim the tremendous complexity of their product renders the manufacture of safe and effective follow-on versions of their biologic impossible without extensive (and financially prohibitive) clinical trials.

[18] Innovator drug sponsor might also consider whether improved bioanalytics will encourage follow-on drug sponsors to petition FDA for recall or reexamination of innovator reference biological drugs due to the inherent "drift" of protein drugs away from their originally approved specifications/indications.

[19] Parties attempting to invalidate and/or design-around patented biologics could argue the opposite.

If you have any questions about this article, or would like to discuss this topic further, please feel free to contact:

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