

Negotiating a New Legal Landscape: The Advent of Follow-On Biologics

By CANDICE DECAIRE, JOHN McDONALD, PH. D.,
CYNTHIA ROTHSCHILD, PH. D., KATHRYN WADE, PH. D
& ALYSON WOOTEN, PHARM. D.*

Introduction

THE MANNER IN WHICH CREATORS of biopharmaceuticals approach research and development, product approval, marketing, and patent protection is undergoing fundamental change in light of new law. Two relatively recent statutes—one providing for approval of and resolution of patent disputes concerning biopharmaceuticals, and the other making changes to basic patent law—outline a new legal framework. Although the parameters of that framework have yet fully to be defined, it is clear that the new law will require biopharmaceutical inventors and manufacturers to focus on patent strategies early in the product planning process by gathering comprehensive information about relevant existing patents and applications, carefully weighing the benefits of applying for patent protection and determining the scope of protection to seek, and considering the consequences of disclosure requirements in connection with obtaining regulatory approval and/or patent protection.

The Biologics Price Control and Innovation Act (“BPCIA”), enacted in March 2010, provides for regulatory approval of “follow-on” biopharmaceuticals and is loosely analogous to the system established for generic drugs.¹ The BPCIA allows for streamlined Food and Drug Administration (“FDA”) approval of “follow-on biologics.” Follow-on biologics (“FOBs”) can be approved more quickly and without substantial investment in clinical trials because they are “highly similar” to

* The authors are attorneys with Kilpatrick Townsend & Stockton LLP. Further information about the authors and Kilpatrick Townsend & Stockton LLP’s pharmaceuticals and biopharmaceuticals practice may be accessed at www.kilpatricktownsend.com.

1. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010).

biologic products that have already been approved by the FDA (“reference biologic products”). The BPCIA also imposes disclosure obligations that may change the manner in which developers of FOBs choose to apply for market authorization. Further, it provides procedures for resolving patent infringement disputes that will require developers of both FOBs and reference biologic products (“RBPs”) to adopt proactive patent strategies. The BPCIA is aimed at encouraging development and dissemination of FOBs at lower cost to patients while protecting investment in innovation.

The America Invents Act (“AIA”), enacted September 16, 2011, makes significant changes to U.S. patent law that will affect the manner in which developers of RBPs and FOBs address development, application for patent protection, and patent disputes. The AIA provides new procedures intended to improve the quality of U.S. patents and to transition the national patent system to one that is consistent with international patent law.² Among other changes, the AIA provides for a “first to file” patent priority system, distinguished from the previous “first to invent” patent priority.³ The AIA also provides revised and new procedures useful to third parties challenging the validity of U.S. patents.⁴ This new legal landscape elevates the importance of careful investigation and planning at early stages in the process of researching and developing biologic products.

It remains to be seen whether the BPCIA as implemented, and along with changes to patent law under the AIA, will achieve its goal of making biologics cheaper and more widely available while maintaining incentives for biologic innovation in the United States. This Article explores the potential consequences of the new legal landscape for biologics manufacturers. Part I provides a general introduction and background concerning (1) the importance of biologics in the U.S. and global markets and (2) the characteristics of biologic products. Part II includes: (1) an overview of the law applicable to follow-on biologics with background on approval pathways other than that established by the BPCIA, (2) a summary of the important provisions of the BPCIA, and (3) a brief discussion of the FDA’s draft guidance concerning specific implementation of the BPCIA. Part III summarizes some of the more significant changes to patent law imple-

2. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

3. § 3(b), 125 Stat. at 285-87 (amending 35 U.S.C. §§ 102-103).

4. § 3(h)-(i), 125 Stat. at 288-90 (providing derivation proceedings); § 6(d), 125 Stat. at 305-11 (amending post grant review proceedings at 35 U.S.C. §§ 321-329); § 6(a), 125 Stat. at 299-305 (amending 35 U.S.C. §§ 311-319).

mented by the AIA and discusses how those changes may affect patent filing strategy, patent prosecution, and resolution of patent disputes in the context of biologics. Finally, Part IV focuses on the practical implications of the new framework, for both RBP and FOB companies.

I. Background

A. General Introduction

Biologics, also known as biological drugs, are pharmaceuticals made from living sources such as bacteria, viruses, cell culture, or animals.⁵ They are one of the most exciting frontiers in therapeutic healthcare and are projected to play an increasingly important role in the pharmaceuticals market. Biopharmaceuticals have been proven as effective therapeutics for diseases and disorders such as colon cancer, multiple sclerosis, and rheumatoid arthritis. Scientific advances show great promise for many additional therapies.

Biologics and biopharmaceuticals are one of the fastest growing and most expensive components of the U.S. prescription pharmaceutical market. Combined sales of the top twelve biologic products in the United States were around \$30 billion in 2010.⁶ It has been predicted that by 2014, seven of the top ten pharmaceutical products will be biologics.⁷ By 2018, sales of prescription biologic products are expected to rise to \$129 billion, up from \$74 billion in 2011.⁸

As discussed *infra*, developing and producing a biologic is generally more expensive and complicated than developing a traditional small molecule drug. Development costs for an innovator biologic product (also termed “reference” or “pioneer” biologics) can exceed \$1.2 billion by market launch of the product.⁹ A biologic innovator that obtains patent protection, for its biologic and/or the processes

5. See, e.g., *Definition of Biological Drug*, NAT'L CANCER INST., <http://www.cancer.gov/dictionary?CdriID=426407> (last visited June 8, 2012).

6. ANDREW F. BOURGOIN, THOMPSON REUTERS, WHAT YOU NEED TO KNOW ABOUT THE FOLLOW-ON BIOLOGIC MARKET IN THE U.S.: IMPLICATIONS, STRATEGIES, AND IMPACT (2011), available at <http://thomsonreuters.com/content/science/pdf/ls/newport-biologics.pdf>.

7. See Press Release, EP Vantage, Biotech Set to Dominate Drug Industry Growth (June 17, 2009), <http://www.evaluatepharma.com/Universal/View.aspx?type=Story&id=188700§ionID=&isEPVantage=yes> (last visited June 21, 2012).

8. EVALUATEPHARMA, SURVEYING TOMORROW'S BIOPHARMA LANDSCAPE: THE NASDAQ BIOTECH INDEX UP CLOSE 4 (2012).

9. Press Release, PhRMA, PhRMA Statement Supporting Fair Incentives for Biologics Innovation (Oct. 19, 2010), available at <http://www.phrma.org/media/releases/phrma-statement-supporting-fair-incentives-biologics-innovation> [hereinafter PhRMA Press Release].

used to create the biologic, is generally able to recoup some of that investment through patent exclusivity.¹⁰ Still, much of the cost is passed along to the patient. Biologic treatment for a single patient can cost tens of thousands of dollars annually.¹¹ For example, Avonex®, which treats multiple sclerosis, has been reported to cost \$20,000 per year; Avastin®, a colorectal cancer therapy, has been reported to cost \$43,000 per treatment course; and Enbrel®, a drug for rheumatoid arthritis, has been reported to cost up to \$25,000 per year.¹² Accordingly, there is a demand for more accessible biologics that can be made available to more patients at a lower cost. The BPCIA was passed, in large part, as a response to this demand.

B. Follow-on Biologics

The availability of traditional chemical or small molecule pharmaceuticals in generic form has successfully lowered costs and made medications more widely available. Generic versions of brand name innovator chemical drugs—versions of the drug that are proven to be substantially the same as the original—are widely available at relatively low cost under the provisions of the Hatch-Waxman Act (“Hatch-Waxman”).¹³ Hatch Waxman allows a generic drug maker to rely on previously submitted safety and efficacy data from the developer of the brand name drug (often termed the “innovator” or “pioneer”).¹⁴ A generic drug maker can take advantage of abbreviated procedures to obtain FDA approval, making generic drugs less expensive than their brand name counterparts. The streamlined procedures provided under Hatch Waxman are applicable only to pharmaceuticals approved under the Food, Drug, and Cosmetic Act (“FD&C Act”) and, as such, do not generally apply to biologics.

Given the demand for more widely available and less expensive biologics, several major world markets (among them, the European Union and Japan) have instituted systems intended to facilitate ap-

10. Exclusivity refers to a specific number of years during which no one may make, sell, offer to sell, use, or import the biologic without permission from the innovator/patent holder.

11. See “Senators Announce Bipartisan Proposal to Bring Biologic Drugs to Market, Saving Billions in Medicare Costs,” *available at* <http://www.collins.senate.gov/public/index.cfm/press-releases?ID=48a978f0-802a-23ad-438c-1d7905e249c0> (last visited June 21, 2012).

12. *Id.*

13. 21 U.S.C. § 355(j) (2006).

14. See *id.* (listing the requirements of the abbreviated new drug application, which substitutes bioequivalence studies for the safety and efficacy studies required in a new drug application under 21 U.S.C. § 505(b)(1)).

proval of “biogenerics” or “biosimilars.”¹⁵ It is estimated that bringing follow on biologics to market would save federal healthcare programs like Medicare and Medicaid at least \$10 billion.¹⁶ However, as discussed in detail *infra*, the complexity of biologics dictates that the legal and regulatory framework for approving a FOB cannot track the Hatch Waxman provisions for approving generic drugs.

With enactment of the BPCIA, the United States made its own provision for approval and marketing of FOBs. Global sales of biosimilar products that would be eligible for the new BPCIA FOB approval pathway are projected to grow to \$3.7 billion by 2015 (up from \$243 million in 2010).¹⁷ This projected market expansion illustrates growing demand for accessible biologics. The growing market for FOBs is also attributed to the fact that market exclusivity for many biologics (under the rules governing FDA application procedures and/or patent protection) will expire in the next few years, opening the door to additional manufacturers.¹⁸ FDA market exclusivity for the biologic products Herceptin® (trastuzumab), Remicade® (infliximab), Rituxan® (rituximab), and Enbrel® (etanercept) expired in 2010; by 2018, Avastin® (bevacizumab), Neulasta® (pegfilgrastim), Humira®

15. Terminology is confusing in this area. What the U.S. law has defined as “follow-on biologics” (FOBs) may also be variously referred to as “biogenerics,” “biobetters,” “biosimilars,” “subsequent entry biologics” (“SEBs”), or “post-patent biologics.” Indeed, the oft-used term “biogeneric” is a misnomer. A generic drug is proven to have the “same” active ingredient and possess the same biological as the brand name product. As discussed *infra*, the complex nature of many biologic products may preclude a conclusive demonstration of such “sameness.” This Article uses the term “follow-on biologic” or “FOB” to avoid confusion and to maintain the distinction that the U.S. law draws between a FOB that is “biosimilar” and a FOB that is “biosimilar” and “interchangeable.” See *infra* Part IV.

16. See, e.g., Donald Zuhn, *President’s Latest Budget Proposal Seeks Decrease of Data Exclusivity Period and Elimination of Pay-for-Delay Agreements*, PAT. DOCS (Feb. 21, 2012), <http://www.patentdocs.org/2012/02/presidents-latest-budget-proposal-seeks-decrease-of-data-exclusivity-period-and-elimination-of-pay-f.html>.

17. Ben Hirschler, *Biosimilars Seen as a \$3.7bln Drug Market by 2015*, REUTERS (Mar. 28, 2011), <http://www.reuters.com/article/2011/03/28/pharmaceuticals-biosimilars-idUSLD E72R0VR20110328>.

18. *Id.*

A patent owner is generally entitled to twenty years of exclusivity, measured from the time of patent filing. 35 U.S.C. § 154(a)(2) (2006).

“FDA market exclusivity” refers to the period of time during which the law and/or FDA regulations provide that the manufacturer who first obtains approval for a particular pharmaceutical is entitled to be the sole authorized source for that pharmaceutical.

For a discussion on exclusivity, see *Frequently Asked Questions on Patents and Exclusivity*, U.S. FOOD & DRUG ADMIN., [http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=exclusivity&utm_content=4#How long is exclusivity granted for?](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm?utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=exclusivity&utm_content=4#How%20long%20is%20exclusivity%20granted%20for%3F) (last updated August 29, 2011).

(adalimumab), and Epogen® (epoetin alfa) also will no longer be entitled to market exclusivity.¹⁹ Patent protection for most of those products will expire by 2015; Avastin® and Humira® retain patent protection until 2018 and 2016, respectively.²⁰ Moreover, once FDA market exclusivity expires, FOB applicants have a substantial incentive to challenge remaining patent protection.²¹

C. The Biologics Price Control and Innovation Act

The BPCIA aspires to balance the need to foster investment in inventing and developing innovator biologics²² with the desire to make FOBs available to more patients at a reduced cost. The BPCIA sets out high-level requirements for a streamlined approval pathway for FOBs and provides an incentive period of market exclusivity for the first-approved FOB.²³ The BPCIA protects the investment of companies who develop and produce reference biologics by providing a market exclusivity period of twelve years after approval of the reference product.²⁴ It provides further protection by setting out thorough procedures for asserting and resolving patent disputes.²⁵ As of the publication of this Article, the FDA has published draft “guidance” documents concerning implementation of the BPCIA, and it has expressly indicated that it will adopt a tiered approach (under which

19. See, e.g., *Eye on Innovation*, DIALOG (Feb. 2011), <http://support.dialog.com/enews/letters/eyeoninnovation/201101/>.

20. See *Patent Term Extensions*, USPTO.GOV, <http://www.uspto.gov/patents/resources/terms/156.jsp> (last visited June 29, 2012).

21. Indeed, a robust body of law has developed around generic drug manufacturers’ challenges to patent protection for small molecule pharmaceuticals under the provisions of the Hatch Waxman Act. A generic manufacturer who wishes to obtain approval under the Abbreviated New Drug Application (“ANDA”) procedure may file a “Paragraph IV” certification, stating that its product does not infringe or that the patents covering the brand name drug are invalid or unenforceable. The advent of FOBs may trigger analogous litigation although, as discussed in this Article, fundamental differences between biologics and small molecule drugs—and in the procedures provided by the BPCIA, as opposed to Hatch Waxman—may result in “higher stakes” litigation with broad scope applicable to particular categories of biologics and biologic formulations.

22. See *supra* note 1 at § 7001(b). Under the BPCIA, an innovator biologic or reference biologic is the initial version of a biologic compound that is made by what is termed the “innovator.”

23. 42 U.S.C. § 262(k).

24. 42 U.S.C. § 262(k)(7)(A) (2006 & Supp. IV 2011). The period of market exclusivity is that period during which no other company may market a FOB for that product.

25. 21 U.S.C. § 355(b)–(c), (j).

testing requirements can and will be specific to a product or product-class).²⁶

II. Characteristics of Biologics

Biologics can include nucleic acid compounds, peptides, proteins,²⁷ antibodies,²⁸ blood products, cells, tissues, nucleic acids such as vectors for gene therapy,²⁹ and small inhibitory ribonucleic acid (“RNA”) molecules,³⁰ and the like. A biologic may be a purified or isolated form of a compound that exists in nature.³¹ For example, a biologic may be a purified peptide or protein formulated as a therapeutic composition. Alternatively, a biologic may be designed to include specific modifications to proteins found in nature to improve the stability (half-life) or the pharmacokinetic profile of the biologic following administration to a patient.

Modifications to a biologic may include amino acid substitutions, glycosylation (addition of a sugar residue), mutation of reactive sites, and fusion to other peptides or proteins. Proteins are encoded in na-

26. U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT, DRAFT GUIDANCE 4–6–8 (2012), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf> [hereinafter SCIENTIFIC CONSIDERATIONS].

27. Proteins and peptides are polymers of amino acids linked to each other. Generally, peptides are shorter polymers (i.e., less than fifty amino acids) than proteins. *See, e.g.*, JEREMY M. BERG ET AL., *BIOCHEMISTRY* 16–23 (W.H. Freeman & Co. 6th ed. 2007).

28. An antibody is a molecule that can react with a component (i.e., often another protein, a bacteria, or a virus) to provide an immune response. Antibodies have a variety of structures. The different portions of the antibody molecule have defined sequences and structure to react either with the foreign component (i.e., the antigen) or the immune cells of the host.

29. The term “vector” or “plasmid” is used in this Article to describe a vehicle that is used to transfer genetic material such as DNA sequences from a donor organism to the target cell of the recipient organism (i.e., from a donor cell to the types of cells that will be cultured to produce a biologic). *See, e.g.*, *Vector*, BIOLOGY ONLINE, <http://www.biology-online.org/dictionary/Vector> (last visited Dec. 26, 2011); *Plasmid*, BIOLOGY ONLINE, <http://www.biology-online.org/dictionary/Plasmid> (last visited Dec. 26, 2011).

30. Small interfering ribonucleic acid (“siRNA”) molecules are RNA molecules that have the ability to bind to certain sites on messenger RNA so as to result in degradation of the mRNA and inhibition of expression of the gene. Andrew J. Hamilton & David C. Baulcombe, *A Species of Small Antisense RNA in Posttranscriptional Gene Silencing in Plants*, 286 *SCIENCE* 950 (1999).

31. *See, e.g.*, U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., GUIDANCE FOR INDUSTRY: QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PROTEIN PRODUCT, DRAFT GUIDANCE 14 (2012), *available at* <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf> [hereinafter QUALITY CONSIDERATIONS] (discussing methods for producing biologics and biosimilars).

ture by an individual's deoxyribonucleic acid ("DNA"). This type of biological synthesis can be replicated in the laboratory by using particular cell lines, inserting a desired sequence of nucleotides (encoded to catalyze production, or "expression," of a desired protein), and thus engineering recombinant DNA constructs capable of synthesizing the protein of interest.

Unlike a small molecule drug, which is generally defined by its chemical composition, a biologic is largely defined by its method of manufacture—typically synthesis by a living cell using the cell's DNA, RNA, and protein synthesis machinery.³² For example, protein therapeutics (the most common biologics) are often produced using recombinant genetic techniques, through which the specific characteristics of the protein may be altered at various stages of the manufacturing process.³³ Using these techniques generally entails isolating a DNA sequence encoding the desired protein.³⁴ Then introducing it into a host cell, which may be a bacterium, yeast, or mammalian cell,³⁵ by using an appropriate vector (i.e., plasmid vector, transposon vector, or viral vector).³⁶

Producing a biologic for the market requires scaling up the cell culture used for production by culturing many liters of cells in conditions under which the cells produce high levels of the desired protein.³⁷ Variations in the methods of culturing the host cells or processing the cell culture medium may affect the therapeutic characteristics of the resulting biologic protein. The protein produced by the cell culture is then tested to ensure the purity and homogeneity of the molecular structure. For example, changing the nature of the cells used, or the cell culture medium, can result in differences in how a

32. See, e.g., *id.* at 4 (comparing small molecule drugs to protein products).

33. *Id.*

34. See 3 JOSEPH SAMBROOK & DAVID W. RUSSELL, *MOLECULAR CLONING: A LABORATORY MANUAL* §§_11.38–.98_ (3d ed. 2001) [hereinafter SAMBROOK & RUSSELL: *MOLECULAR CLONING*]; see also JOSEPH SAMBROOK & DAVID W. RUSSELL, *THE CONDENSED PROTOCOLS FROM Molecular Cloning: A Laboratory Manual* 599–620 (2006).

35. For example, Chinese Hamster Ovary (CHO) cells are often used to make mammalian proteins.

36. A viral vector is a vector that utilizes viral sequences, at least in part, for replication and/or expression of the DNA of interest. See, e.g., Philip M. Arlen et al., *Vaccines for the Treatment of Cancer*, in *HANDBOOK OF ANTICANCER PHARMACOKINETICS AND PHARMACODYNAMICS* 457, 461 (William D. Figg & Howard L. McLeod eds., 2004). A transposon vector is a vector that uses transposon sequences to insert the DNA which may encode the biologic protein of interest into a genome. See, e.g., GEORGE P. RÉDEI, *ENCYCLOPEDIA OF GENETICS, GENOMICS, PROTEOMICS AND INFORMATICS* 2023 (3d ed. 2008).

37. See generally BJORN K. LYDERSEN, *LARGE SCALE CELL CULTURE TECHNOLOGY* (1993) (discussing methods of large scale cell culture used in biotechnology).

particular protein is modified (i.e., by glycosylation and/or other modifications).³⁸ Such changes may be silent (not detected in terms of the biological function of the molecule) or may result in significant alterations in the structure and/or biological activity of the protein. Also, at least some degradation may occur due to instability of the protein in culture or during the purification process.³⁹

Methods used for formulation of a biologic in a form for use as a therapeutic agent also may significantly affect the stability and/or efficacy of the biologic. For example, a protein biologic may be provided as a lyophilized (freeze-dried) formulation. However, finding mixtures of components that preserve the stability and/or activity of a complex molecule, such as a protein in this state, may require significant testing.⁴⁰ In contrast, formulations for small molecule compounds tend to be far less unpredictable.⁴¹

A. A Biologic May Be Highly Complex

Biologics are typically far larger and more complex than small molecule chemical drugs. Small molecule drugs are often organic compounds with a molecular backbone ranging from three to ten atoms of carbon (in some cases including nitrogen, sulfur, and/or oxygen atoms) with side chains comprised of carbon, nitrogen, oxygen, and hydrogen. Small molecule therapeutics are generally single molecular units with a limited number of reactive sites per molecule. In contrast, biologics are often polymers (chains of multiple molecules), with multiple, and often complex, subunits.⁴²

The added complexity of biologics introduces far more potential for variation and a corresponding decrease in predictability of the effects of modifications to the biologic. For example, a monoclonal an-

38. For example, certain cell lines may naturally produce enzymes that can cleave the protein of interest at certain sequences in the protein molecule. Also, certain cell lines may have enzymes that can be activated if a protein is glycosylated (i.e., has a sugar residue) at a certain position.

39. Testing for whether such degradation has occurred may be performed by experiments to measure the size of the protein(s) produced by the cell culture. Degradation products (which are smaller than the full-length protein) are detected as smaller contaminants. See 3 SAMBROOK & RUSSELL: MOLECULAR CLONING, *supra* note 34, § 17.78.

40. See, e.g., QUALITY CONSIDERATIONS, *supra* note 31, at 14.

41. Factors important to the stability of smaller molecules are not, however, trivial. Such factors may include crystal structure and the solvate (e.g., NaCl vs. water) used to form the crystals and whether such salts are interchangeable as well as the presence of polymorphs and other modifications of the chemical structure.

42. See, e.g., QUALITY CONSIDERATIONS, *supra* note 31, at 4 (comparing small molecule drugs to protein products).

tibody may include about 1500 amino acids, some of which could be modified and/or substituted with a similar amino acid (for example, an alanine for valine substitution) without significantly altering the pharmacological activity of the antibody. On the other hand, a relatively small modification, such as glycosylation (addition of a sugar molecule) at a specific amino acid, may have significant effects such as increasing or decreasing the stability of the antibody *in vitro* (as formulated and sold) or *in vivo* (in cell-culture during production or in a patient).

B. Achieving and Establishing Sufficient “Similarity” to a Reference Biologic Product May Be Difficult

It is readily apparent that development of a FOB is not as simple as developing a generic, small molecule drug. Developing a generic, small molecule drug is straightforward. The process entails chemical synthesis by a known and precise method to create, purify, and formulate a drug with a known formula in a suitable and stable dosage form.⁴³ Safety and efficacy can be established by verifying that the active ingredient is chemically identical to the active ingredient in the brand name drug.⁴⁴

Ensuring that a FOB has the same, or sufficiently similar structure, stability, and biological activity as a RBP may require much the same level of effort as developing the RBP. Because the synthesis of a biologic utilizes complex biological systems, it is expected that changes to any of the steps used for synthesis (i.e., modifications to the protein sequence, cells, and/or culture conditions) would lead to a need for substantial testing to verify that changes to any of the required steps do not adversely affect the structure and activity of the FOB.

To characterize a proposed FOB accurately, an applicant must identify its sequence and three-dimensional structure. The applicant must also analyze whether and how any differences in sequence or three-dimensional structure between the FOB and the RBP will affect the FOB’s pharmacological activity, or its safety. It is critical that the applicant identifies any change in a FOB—including a substitution of a single amino acid in a complex protein—and test the FOB to determine whether the change affects pharmacological activity or safety. Analyzing the nature of a RBP, or the effect of any change between

43. *Id.*

44. *See infra* Part III.B (discussing the ANDA approval process).

the RBP and a FOB, will require a variety of tests, potentially including amino acid or nucleic acid sequencing, mass spectrometry, testing of immunogenicity and toxicity *in vivo*, stability and binding studies *in vitro*, and pharmacokinetic testing.

A peptide or protein comprises a particular sequence of amino acids. Any change in that sequence will change the primary structure of the protein and may significantly affect the manner in which the protein functions.⁴⁵ A peptide (simple protein), for example, may be comprised of four amino acids: methionine (M); alanine (A); proline (P); and isoleucine (I). However, a peptide having the sequence M-A-P-I could be entirely different in structure and function than a peptide having the sequence I-P-A-M. Thus, determining the composition and structure of a protein requires the chemical characterization of the component amino acids in sequence (“sequencing”) and identification of the composition and location of molecules that may be attached to those component amino acids.

Studies must be performed to determine how the biologic will function when administered to a patient. Whether a biologic will bind to its intended effector molecule (i.e., a receptor or other reactive molecules) can be determined through *in vitro* tests so as to measure binding affinity of the biologic for its target.⁴⁶ Pharmacokinetic testing is performed to determine the rate of breakdown of the biologic in the patient. These tests are used to determine the effective concentration, dose, and duration of treatment.⁴⁷ Immunogenicity—the extent of a patient’s immune response to administration of the biologic—must also be considered and may be predicted by performing tests in animals,⁴⁸ although a conclusive determination of immunogenicity in humans may require substantial clinical testing.⁴⁹

To determine whether a proposed FOB is sufficiently similar to the RBP so as to benefit from testing that has established safety and efficacy of the RBP, the FOB must be evaluated under conditions of cell culture used for production and processing similar to what was required for the reference biologic. This is complicated by the fact that the RBP innovator is unlikely to share its master cell bank. The aspiring FOB manufacturer may use different cells, but nonetheless must develop cell culture conditions that result in high levels of pro-

45. See, e.g., SCIENTIFIC CONSIDERATIONS, *supra* note 26, at 4–5.

46. *Id.* at 12.

47. SCIENTIFIC CONSIDERATIONS, *supra* note 26, at 15.

48. See, e.g., *id.* at 13–14.

49. See *id.* at 14–16.

duction of a stable and pure form of the FOB that performs in a manner “highly similar” to the RBP.

Moreover, a FOB developer has an incentive to try to “design around” the innovator’s patent protection—that is, to attempt to make a minor change to its processes and/or FOB to avoid infringing on the innovator’s patent rights to the FOB itself or to the method of making the FOB. In the context of biologic products, such relatively minor changes may fundamentally affect the therapeutic properties of the FOB. Those changes could result in improved therapeutic properties (i.e., improved pharmacokinetics or stability), but just as easily could cause problems—untoward effects such as unanticipated immune responses.

FOBs that can be made available to the public relatively quickly at an affordable price by avoiding lengthy and expensive development and testing, may, at least for more complex biologics, be an elusive goal. The approval process for FOBs cannot be defined in terms of bright line, “one fits all” rules because a single biologic protein is a compilation of individual amino acids, some of which are essential to therapeutic activity and safety, and others of which may be changed without affecting efficacy or safety. The BPCIA recognizes this complication and grants the FDA broad discretion both to determine what proposed products may be eligible for the FOB application process and what types and amounts of test data will be required to support an application.⁵⁰ The FDA has indicated that application eligibility and requirements will vary by product class.⁵¹ It is possible that FOB applications will not be permitted for some classes of biologic products where concerns about potential health and safety risks outweigh the desirability of increasing product availability or accessibility.⁵²

III. Overview of Previous Approval Routes Available for Some Biological Pharmaceuticals

A. Initiating the Approval Process

The approval process for a NDA and Biologics License Application (“BLA”) begins with an Investigational New Drug Application (“IND”) designed to impose analytical, nonclinical, and clinical research requirements that support the compound’s safety and effi-

50. See 42 U.S.C. § 262(k)(3) (2006 & Supp. IV 2011).

51. See *id.* § 262(k)(8); see also SCIENTIFIC CONSIDERATIONS, *supra* note 26.

52. See 42 U.S.C. § 262(k)(8).

cacy.⁵³ An applicant must analyze and characterize the composition and structure of the compound.⁵⁴ The compound is then tested, both *in vivo* (within an intact organism) and *in vitro* (in solution or within cultured cells of relevant animal species), to evaluate bioavailability, toxicity, and other functional characteristics.⁵⁵

A compound that demonstrates therapeutic potential and safety in animal studies is subsequently studied in humans.⁵⁶ Human clinical trials are subject to strict parameters and proceed in several phases.⁵⁷ Phase I trials administer the compound to healthy subjects to determine its safety in humans.⁵⁸ Phase II trials administer the compound to patients with a specific condition or disease to determine its therapeutic effect, safety, and lack of harmful side effects.⁵⁹ Phase III trials establish the therapeutic efficacy of the compound.⁶⁰ This phase of studies includes a larger number of patients, and the compound is typically administered to several groups of patients with the specific condition or disease over defined periods of time.⁶¹ If the FDA finds the data from Phase I, II, and III trials to be acceptable, the compound will be approved for marketing.⁶² Post-marketing evaluation—Phase IV studies—is used further to assess whether the compound is an effective treatment, to track patient outcomes and to identify and assess any side effects or safety risks.⁶³

The detailed and extensive studies required to support an IND application require large investments of time and money. A compound is not generally available to patients until Phase III trials are complete, which may take over ten years.⁶⁴ Accelerating the marketing approval process where feasible would make beneficial compounds sooner available to patients. Streamlining research and investigation requirements likewise benefits patients—lower development costs would ostensibly lead to lower prices.

53. 21 U.S.C. § 355 (2006).

54. *Id.* § 355(b)(1).

55. *Id.* § 355(b)(1)(A).

56. *Development & Approval Process (Drugs)*, *supra* note 18.

57. *Understanding Clinical Trials*, CLINICALTRIALS.GOV, <http://clinicaltrials.gov/ct2/info/understand> (last updated Sept. 20, 2007).

58. 21 C.F.R. § 312.21 (2011).

59. *Id.*

60. *Id.*

61. *Id.*

62. *Understanding Clinical Trials*, *supra* note 57.

63. 21 C.F.R. § 312.85.

64. Steven M. Paul et al., *How to Improve R&D Productivity: The Pharmaceutical Industry's Grand Challenge*, 9 NATURE REV. DRUG DISCOVERY 203, 211 (2010).

B. Federal Food, Drug and Cosmetic Act Versus Public Health Services Act

The data collected during the IND process is used to support a NDA or a BLA. A NDA is filed under the Federal Food, Drug, and Cosmetic Act (“the FD&C Act”); however, a biologic can be approved under both the FD&C Act⁶⁵ or the Public Health Services Act (“PHSA”).⁶⁶ These two acts are different. The FD&C Act applies to all drugs and medical devices, while the PHSA applies to biological products.⁶⁷ The FDA administers both statutes.⁶⁸

A NDA allows for marketing approval for a pharmaceutical covered by the FD&C Act.⁶⁹ A BLA allows for approval of a new biologic regulated by the PHSA.⁷⁰ Accelerated approval pathways for NDA approved products are available for (1) “generic” products that are proven through an Abbreviated New Drug Application (“ANDA”) application to be the “same” as the previously approved product; and (2) modifications of the previously approved product that are shown through a section 505(b)(2) application to be appropriately supported by the FDA’s findings with respect to the previously approved product.⁷¹

Historically, there has been some overlap between biologics subject to the PHSA and drugs regulated under the FD&C Act.⁷² “On June 30, 2003, the FDA transferred some of the therapeutic biological products that had been reviewed and regulated by the Center for Biologics Evaluation and Research (“CBER”) to the Center for Drug Evaluation and Research (“CDER”).”⁷³ CDER is responsible for the following categories of biologics: monoclonal antibodies for *in vivo* use; most proteins intended for therapeutic use; immunomodulators;

65. 21 U.S.C. §§ 301–399D (2006).

66. 42 U.S.C. § 262 (2006 & Supp. IV 2011).

67. 21 U.S.C. § 393; 42 U.S.C. § 241.

68. 21 U.S.C. § 393; 42 U.S.C. § 241 (providing that the Secretary of the Department of Health and Human Services is responsible, acting through the FDA Commissioner, for executing the FD&C Act).

69. 21 U.S.C. § 355(b)(1).

70. 42 U.S.C. § 262.

71. 21 C.F.R. § 320.24 (2011).

72. Human Drugs Which Are Biological Products, Redefinition of Authority to Administer Certain Provisions of the Federal Food, Drug, and Cosmetic Act, 37 Fed. Reg. 4004, (Feb. 25, 1972).

73. *Transfer of Therapeutic Products to the Center for Drug Evaluation and Research*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CBER/ucm133463.htm> (last updated Feb. 22, 2010).

growth factors; and cytokines.⁷⁴ Other biologics, including cellular products, gene therapy products, vaccines, allergenic extracts, antitoxins, blood, and blood components, remain under CBER.

C. Accelerated Approval Pathways Before the Biologics Price Competition and Innovation Act

Before passage of the BPCIA, the law provided two accelerated routes to approval of compounds for which it can be shown that previous studies in connection with an NDA. Hatch Waxman provides for an ANDA⁷⁵ for generic versions of pharmaceuticals regulated under the FD&C Act, and Section 505(b)(2) of the FD&C Act provides a somewhat accelerated application process for pharmaceuticals that may not be eligible for an ANDA.⁷⁶

1. Abbreviated New Drug Application

To qualify for ANDA approval, an applicant must show that the proposed product (the generic) is a pharmaceutical equivalent to the product that was approved under the full NDA application procedure—i.e., subject to the IND requirements (the “brand name,” “reference,” “pioneer,” or “innovator” product).⁷⁷ The statute speaks in terms of “sameness” and contemplates that a generic product approved by the ANDA process will be essentially identical to the reference product.⁷⁸ An ANDA applicant must provide chemical and bioequivalence data showing that its product has the same amount of the same active ingredient in a dosage form that makes the active ingredient “bioavailable” (released within the patient) at the same rate and to the same extent as the product already approved by the FDA.⁷⁹ If *in vivo* and *in vitro* studies support that the bioavailability and purity levels of the ANDA applicant’s formulation of the active ingredient are the “same” (within tightly defined acceptable limits), the products

74. *Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113522.htm> (last updated Dec. 24, 2009).

75. An Abbreviated New Drug Application (“ANDA”) contains data that permits the approval of a generic, or bioequivalent, drug. *Abbreviated New Drug Application (ANDA): Generics*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/default.htm> (last updated Jan. 3, 2012).

76. 21 U.S.C. § 355 (2006).

77. 21 C.F.R. pt. 320 (2011).

78. *Id.*

79. *Id.*

will be treated as therapeutically equivalent.⁸⁰ The ANDA applicant can then rely on preclinical and clinical trials that established safety and efficacy of the brand name product.⁸¹ A generic drug approved under the ANDA process will be automatically substitutable for the brand name product without physician intervention.⁸²

2. Section 505(b)(2)

Section 505(b)(2) was added to the FD&C Act in 1984 to avoid duplicative testing and Phase III human studies for products that are reformulations or combinations of existing approved drugs.⁸³ A product may be approved by the 505(b)(2) “paper NDA” pathway if it is shown to be largely the same as products that have already completed the NDA process.⁸⁴ Section 505(b)(2) is applicable to proposed modifications of previously approved “drugs,” broadly defined, and unlike ANDA provisions, does not require proof that the product applied for is the “same” as the reference product.⁸⁵ Modifications for which 505(b)(2) approval may be sought include changes in dosage form, indication or formulation, and extend to changes in active ingredients where only limited clinical data is necessary to show that the product incorporating the changed ingredient is therapeutically equivalent to the product that is already approved.⁸⁶ Products eligible for the 505(b)(2) process include biologics that were initially approved through an NDA.⁸⁷ The amount of data required to support a 505(b)(2) application varies according to the product modification at issue, but the 505(b)(2) approval pathway generally falls somewhere between onerous NDA requirements and a streamlined ANDA showing.⁸⁸

80. 21 C.F.R. § 320.24.

81. *Id.*

82. U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (2012), available at <http://www.fda.gov/cder/orange/obannual.pdf> [hereinafter ORANGE BOOK].

83. U.S. DEP’T OF HEALTH & HUMAN SERVS. ET AL., GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(B)(2), DRAFT GUIDANCE (1999), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079345.pdf> [hereinafter APPLICATIONS COVERED BY 505(B)(2)].

84. *Id.*

85. *Id.*

86. 21 C.F.R. § 314.54.

87. *Id.* § 314.3(b); see Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872 (July 10, 1989) (to be codified at C.F.R. pts. 10, 310, 314, 320).

88. APPLICATIONS COVERED BY 505(B)(2), *supra* note 83.

An applicant must demonstrate the “relevance and applicability” of the FDA’s findings with respect to the reference product. Depending on the product at issue, the FDA may also require the applicant to provide clinical data, including data from human trials, to show that any differences do not affect therapeutic efficacy or safety.⁸⁹ Successful applicants under section 505(b)(2) are entitled to market exclusivity of three to five years.⁹⁰ The length of market exclusivity granted depends on the nature of the product modification that was approved and the amount of clinical data supporting such modification.⁹¹

D. Pre-Biologics Price Competition and Innovation Act Approval Routes for Modification of Products Approved Under a Biologics License Application

1. Supplemental Biologics License Application

A reference biologic is approved on the basis of the information required to support a BLA—that is, data concerning the structure and composition of the biologic and its method of manufacture, pre-clinical studies, clinical studies, and labeling. After obtaining that approval, a biologics manufacturer can seek approval for new indications (new therapeutic uses), labeling changes, or changes in the method of manufacture by submitting a Supplemental Biologics License Application (“sBLA”). sBLAs are also used to seek approval for post-marketing studies or to submit additional safety or efficacy data for FDA review.

The regulation providing for sBLAs classifies changes according to the degree to which they might be expected to affect the therapeutic efficacy and safety of a biologic. Some changes require FDA approval before any modified product (which includes product manufactured by a modified process) may be distributed; other changes simply require reporting to the FDA in a special submission or in an annual report. Changes requiring submission and approval of an sBLA, which must be supported by testing and data over and above what was originally submitted to support the BLA, include “any change in the product, production process, quality controls, equipment, facilities, or responsible personnel that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effective-

89. *Id.*

90. 21 U.S.C. § 355(j)(5)(F) (2006).

91. *Id.*

ness of the product.” Specific examples of such changes include changes to product components (active or inactive ingredients), changes to specifications for use of the product in its previously approved applications, changes in the source tissue or cell, establishment of a new master cell bank, and changes in product purification and sterilization procedures.

2. Product “Comparability”

The FDA issued guidance on a “comparability” standard that applicants may use to establish efficacy, safety, purity, and potency without conducting a full battery of tests and studies that would otherwise be necessary to support approval of a product that is not “comparable” to a previously approved product.⁹² If the FDA determines that a proposed modification results in a product that is “still safe, pure, and potent,” then the modified product is sufficiently “comparable” to be distributed.⁹³

In practice, there is some uncertainty about what is required to demonstrate the requisite comparability. The FDA’s 1996 “Guidance Concerning Demonstration of Human Biological Products, Including Therapeutic Biotechnology-derived Products” explicitly notes that a manufacturer may demonstrate “product comparability,” between a biologic made after a modification and a biologic made before the change was implemented, “through different types of analytical and functional testing, with or without preclinical animal testing.”⁹⁴ The FDA’s guidance describes types of analytical and functional testing, the results of which “determine the extent of additional tests needed,” and further notes:

In cases where a manufacturing change(s) results in a product with structural and/or bioactivity differences, and/or differences in pharmacokinetics patterns, and those differences are meaningful with respect to potential impact on a product’s safety, purity, or potency (efficacy), an additional clinical study(ies) usually may be needed to evaluate the product’s safety and/or efficacy. Additionally, when the analytical and other preclinical testing is not sufficiently sensitive or broad enough to detect such meaningful differences, additional clinical study(ies) may be needed.⁹⁵

92. U.S. FOOD & DRUG ADMIN. . DEMONSTRATION OF COMPARABILITY OF HUMAN BIOLOGICAL PRODUCTS, INCLUDING THERAPEUTIC BIOTECHNOLOGY-DERIVED PRODUCTS (1996), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm122879.htm>.

93. *Id.*

94. *Id.*

95. *Id.*

The FDA reserves the right to determine instances in which no clinical studies are necessary, but “[i]n other instances, the FDA may determine, on the basis of comparability data, that a clinical efficacy study(ies) is necessary.”⁹⁶

IV. Approval Under Section 351(k) – The Biologics Price Competition and Innovation Act

A. Section 351(k) and Implementing Guidelines

The BPCIA—intended to provide a streamlined pathway for approval of FOBs and to address commercial and patent exclusivity issues—was enacted on March 23, 2010 as Section 351(k) of the PHS Act.⁹⁷ The BPCIA opens the door to an accelerated and less burdensome approval process for FOB applicants. It permits reliance on data used to support the RBP application with proof of sufficient similarity to justify extrapolating the RBP data to the FOB.⁹⁸ In this manner, the BPCIA is analogous to the Hatch Waxman provisions for generic drugs. However, just as biologic products differ from small molecule pharmaceuticals, the BPCIA pathway is significantly different from the Hatch Waxman provisions in terms of approach and timing.

Under the Hatch Waxman framework, the FDA rates generic drugs as “therapeutically equivalent” to a previously approved drug if the applicant establishes that the generic is both (1) bioequivalent and (2) pharmaceutically equivalent, to the reference drug.⁹⁹ The testing necessary to demonstrate these standards is well known and fairly predictable. Based on the results of this testing, the FDA assigns each pharmaceutical a therapeutic equivalence designation that indicates the level or degree of “therapeutic equivalence.”¹⁰⁰

The standard and testing necessary to show “therapeutic equivalence” of a FOB, on the other hand, is not predictable. The FDA has broad discretion to control the approval pathway for specific FOBs, or defined classes of FOBs, and is expected to implement final guidelines in the very near future.¹⁰¹ The FDA’s recent draft guidelines shed light on the tiered, product specific approach the FDA intends to ap-

96. *Id.*

97. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001–7003, 124 Stat. 119, 804–21 (2010).

98. 42 U.S.C. § 262(k)(2)–(4) (2006 & Supp. IV 2011).

99. See ORANGE BOOK, *supra* note 82, at vii.

100. *Id.* at xiii–xix.

101. See 42 U.S.C. § 262(k)(8).

ply to approval of FOBs.¹⁰² However, many key issues remain unclear in light of the draft guidance. These issues include the scope of analytical, preclinical, and clinical trial data required to support a FOB application for particular products or product classes; the actual burden of post-marketing risk management and tracking plans for data demonstrating long-term safety and addressing immunogenicity; and the FDA's definition of equivalence, in terms of the "biosimilar" and "interchangeable" standards set out in the statute. It also remains unclear what the standard for finding patent infringement will be and how data and market exclusivity will be applied for the RBP innovator and the FOB applicant. In addition, the FDA still must establish particularized procedures for maintaining the confidentiality of the FOB applicant's particularized information about its proprietary manufacturing processes, which are required to be disclosed to the RBP innovator. It is possible that at least some of these issues will be addressed once this new biologic approval pathway begins to be used by FOB applicants.

B. "Biosimilar" and "Interchangeable"

A FOB can be approved for marketing under the BPCIA if it is proven to be (1) "biosimilar" to or (2) "interchangeable" with the RBP.¹⁰³ A product is "biosimilar" if it is "highly similar to the reference product, notwithstanding minor differences in clinically inactive components,"¹⁰⁴ and "there are no clinically meaningful differences" between the proposed FOB and the RBP "in terms of the safety, purity, and potency of the product."¹⁰⁵ A product is "interchangeable" if it is biosimilar to the RBP and can be expected to produce the same result in any given patient as the RBP.¹⁰⁶ Interchangeability requires that the risk of switching between the RBP and the FOB must not be any greater than the risk of using the RBP alone.¹⁰⁷

1. "Biosimilar"

A FOB applicant must first establish that its proposed product is sufficiently similar to the RBP to warrant licensure under section (k) application process.¹⁰⁸ Analytical studies that demonstrate similarity of

102. See, e.g., SCIENTIFIC CONSIDERATIONS, *supra* note 26.

See, e.g., *id.*

103. 42 U.S.C. § 262(k)(2)-(4).

104. *Id.* § 262(i)(2)(A).

105. *Id.* § 262(i)(2)(B).

106. *Id.* § 262(k)(4)(A)(i)-(ii).

107. *Id.* § 262(k)(4)(B).

108. *Id.* § 262(k)(2)-(4).

a protein in terms of component amino acids and protein structure will likely fulfill this requirement.¹⁰⁹ The BPCIA explicitly contemplates that the FDA may determine that a particular proposed FOB, or even any proposed FOB in a particular class of products, is ineligible for consideration if “science and experience” support that conclusion.¹¹⁰

Once the sufficient similarity is demonstrated as to the RBP’s composition and structure, animal studies may then be required in order to demonstrate toxicity (or lack thereof) and bioavailability of the FOB.¹¹¹ The FDA also may require human clinical studies to evaluate pharmacokinetics in patients and to address immunogenicity concerns.¹¹² Sufficient data must be provided to the FDA to demonstrate that the safety, purity, and potency of the FOB is “highly similar” to that of the RBP for at least one of the uses for which the RBP is authorized (and for which the FOB is proposed to be used).¹¹³ Notably, the FDA may opt to waive requirements for analytical, preclinical, or clinical studies for any particular FOB application.¹¹⁴ The FDA indicated that it expects a science-driven determination as to which requirements are necessary for particular FOBs.¹¹⁵ This gives rise to uncertainty because it means that requirements for demonstrating similarity will be determined on a case-by-case basis.

Establishing that a proposed FOB is “highly similar” to a RBP, in order to establish that the FOB is “biosimilar” under the BPCIA, requires also that sufficient data is provided to show that:

- The FOB and the RBP use the same “mechanism or mechanisms of action” for the conditions of use for which the FOB is proposed (with the caveat that this requirement applies only to the extent that science is able to determine the mechanism of action for the RBP and FOB);¹¹⁶

109. These analytical studies may include, for example, sequencing analyses, biochemical analyses, and immunochemical analyses.

110. 42 U.S.C. § 262(k)(8)(E)(i)–(iii).

111. *Id.* § 262(k)(2)(A)(i)(I)(aa)–(bb).

112. *Id.* § 262(k)(2)(A)(i)(I)(cc). The draft guidance suggested that the need for and scope of clinical studies required may depend on the uncertainty left regarding the biosimilarity of the FOB to the RBP in light of the data from the structural and animal studies. See SCIENTIFIC CONSIDERATIONS, *supra* note 26, at 12.

113. See 42 U.S.C. § 262(k)(2)(A)(ii).

114. *Id.*

115. Margaret A. Hamburg, Comm’r of Food & Drugs, Remarks at the Generic Pharmaceutical Association Annual Meeting (Feb. 18, 2010), available at <http://www.fda.gov/NewsEvents/Speeches/ucm201833.htm>.

116. 42 U.S.C. § 262(k)(2)(A)(i)(II).

- The FOB is proposed for conditions of use for which the RBP has been approved;¹¹⁷
- The FOB is proposed for the same route of administration, dosage form, and strength (concentration) as previously approved for the RBP;¹¹⁸ and
- The FOB is manufactured in a facility that meets FDA standards for safe, pure, and potent manufacture of biologics.¹¹⁹

These data provide the FDA with sufficient information to predict whether the FOB will likely be safe for the proposed use. The FDA still requires that additional data be provided to establish that a FOB is interchangeable with the RBP.

2. “Interchangeable”

Establishing that a “biosimilar” proposed FOB is “interchangeable” will require additional preclinical and clinical studies in all cases, except where the RBP and proposed FOB can be demonstrated to be identical in composition and structure.¹²⁰ As discussed in Part I.B, demonstrating “sameness” of composition and structure is challenging in the context of biologics, for which any small change in composition, structure, inactive components, and/or conditions of manufacture, formulation, handling, or storage may affect the therapeutic activity of the pharmaceutical product.¹²¹ In contrast, in the context of small molecule drugs, a product is automatically determined to be “interchangeable” once structural identity and bioequivalence are shown.¹²² For biologics, however, where seemingly small changes in process may result in significant changes to the properties of the molecule, “interchangeability” cannot be assumed—hence the ostensibly more forgiving “biosimilar” standard.¹²³

C. Preserving Incentives for Reference Biologic Product Innovation

A pharmaceutical innovator is entitled to a period of exclusivity—a time during which no other manufacturer may go to market with a

117. *Id.* § 262(k)(2)(A)(i)(III).

118. *Id.* § 262(k)(2)(A)(i)(IV).

119. *Id.* § 262(k)(2)(A)(i)(V).

120. SCIENTIFIC CONSIDERATIONS, *supra* note 26, at 11; see also 42 U.S.C. § 262(k)(4).

121. See *supra* Part I.B; see also SCIENTIFIC CONSIDERATIONS, *supra* note 26, at 4–6 (noting that minor structural differences can affect a protein’s safety, purity, or potency).

122. See ORANGE BOOK, *supra* note 82, at vi–vii.

123. 42 U.S.C. § 262(i)(2)(A).

generic small molecule drug or a FOB.¹²⁴ This period of exclusivity rewards the innovator for the time and expense of developing the reference pharmaceutical product.

As discussed above in Part I.A, the cost to develop and produce a traditional small molecule drug is significantly less expensive and complicated than developing and producing a biologic drug. Although exclusivity for the innovator is provided for both small molecule drugs (i.e., through the Hatch Waxman Act) and for RBPs (i.e., through the BPCIA), the terms for these exclusivity periods are quite different. The BPCIA gives due weight to the massive investment required to develop a RBP by providing exclusivity periods that protect a RBP innovator's ability to recover that investment.¹²⁵ No FOB application may be filed until four years after a RBP has been approved,¹²⁶ and no FOB application may be approved until twelve years after approval of the RBP.¹²⁷ A RBP may be entitled to another six months of market exclusivity if the manufacturer has conducted the additional studies required to support pediatric use.¹²⁸ A RBP manufacturer is thus guaranteed a minimum of twelve years of market exclusivity during which no FOB may be marketed regardless of whether the RBP's patent protection extends to cover that entire time period.¹²⁹

The Hatch Waxman Act also provides a similar data exclusivity period for new drugs, although the shorter period of exclusivity reflects the typically less complicated development of the small mole-

124. See 21 U.S.C. § 355(c)(3)(E)(ii) (2006); 42 U.S.C. § 262(k)(7).

125. 42 U.S.C. § 262(k)(7).

126. *Id.* § 262(k)(7)(B). A RBP that has been designated for treatment of a rare disease or condition is entitled to seven years exclusivity. See 21 U.S.C. § 360cc(a); see also 42 U.S.C. § 262(m)(2)(B) (providing seven years six months exclusivity when approved for pediatric use).

127. *Id.* § 262(k)(7)(A).

128. *Id.* § 262(m)(2).

129. There has been some debate regarding whether the twelve-year "exclusivity" period granted to the RBP in section (k)(7)(A) refers to "market" exclusivity or "data" exclusivity. That is, some parties have argued that an application may be approved prior to the expiration of the twelve years if the section (k) applicant submits its own clinical data, rather than relying on the data submitted to gain approval of the RBP. Letter from Sen. Kay R. Hagan et al. to Margaret Hamburg, Comm'r, U.S. Food & Drug Admin. (January 7, 2011), available at <http://www.hpm.com/pdf/1-7-11%20Senate%20Biologics%20letter%20to%20FDA.pdf>. Other parties have argued that the twelve-year period provides market exclusivity, in that no section (k) application may be approved, regardless of whether it relies on clinical data from the RBP. Letter from AARP et al. to Margaret Hamburg, Comm'r, U.S. Food & Drug Admin. (January 21, 2011), available at <http://www.hpm.com/pdf/generics%20biosimilars%20letter.pdf>. Regardless of the interpretation, the practical outcome is effectively twelve years of market protection, as the cost to a section (k) applicant to conduct its own clinical studies most likely would be cost prohibitive.

cule drug than that of the RBPs.¹³⁰ For example, it may rely on fewer preclinical and clinical trials for safety and efficacy. While generic manufacturers may borrow the innovator's clinical trial data under the Hatch Waxman Act, a generic manufacturer must wait five years after the approval of the new innovator drug before filing an application that relies on such data for approval.¹³¹ The data exclusivity period, if effective, provides market protection from generic competition. Without access to the innovator's data, a generic manufacturer would have to run its own clinical trials, and the high costs of clinical trials deter market entry.

D. Encouraging Follow-on Biologic Applicants

Because the costs to develop and produce generic versions of traditional small molecule drugs differ from those associated with the production of biologics, the exclusivity period provided by the Hatch Waxman Act for a generic small molecule product and by the BPCIA for a FOB also differ. The Hatch-Waxman Act provides a 180-day market exclusivity period for the first approved generic small molecule drug product.¹³² By contrast, the BPCIA statute encourages FOB applications by awarding a longer market exclusivity period for the first-approved interchangeable FOB.¹³³ That is, no subsequent interchangeable FOB for a particular RBP may be approved for commercial marketing until the earliest of several events:

- “[One] year after the first commercial marketing of the first interchangeable” FOB;¹³⁴
- Eighteen months after a final court decision on all patents in a patent infringement action filed against the FOB applicant, or dismissal of that action;¹³⁵
- Forty-two months after approval of the first interchangeable FOB if the FOB applicant was sued for infringement and the suit is ongoing;¹³⁶ or

130. See, e.g., PhRMA Press Release, *supra* note 9.

131. 21 U.S.C. § 355(c)(3)(E)(ii) (2006).

132. *Id.* § 355(j)(5)(B)(iv).

133. 42 U.S.C. § 262(k)(6) (2006 & Supp. IV 2011).

134. *Id.* § 262(k)(6)(A).

135. *Id.* § 262(k)(6)(B).

136. *Id.* § 262(k)(6)(C)(i).

- Eighteen months after approval of the first interchangeable FOB if the FOB applicant has not been sued for patent infringement.¹³⁷

By providing this longer period of market exclusivity for the first interchangeable FOB, the FDA encourages companies to invest money and resources in the development of FOBs.

E. Patent Protection and Disputes

The BPCIA also expressly addresses the issue of patent protection. A patent provides its owner with the right to exclude others from making, using, or selling the patented invention.¹³⁸ When a RBP innovator obtains a patent for a biologic, or for the process that creates the biologic, the RBP innovator is entitled to a certain number of years of patent protection. During that period of patent protection, companies may not manufacture, sell, offer to sell, use, or import the biologic or process without a license from the RBP.¹³⁹ Given that development of a RBP may take many years, and that a patent application need not be filed until it is “reduced to practice,”¹⁴⁰ the period of patent and market exclusivity does not necessarily coincide. Market exclusivity provisions are intended to ensure that an innovator’s investment is rewarded regardless of patent protection—given that the scope, validity, and enforceability of patents can be challenged via expensive and burdensome litigation.¹⁴¹ Moreover, depending on the

137. *Id.* § 262(k)(6)(C)(ii). The exclusivity provision for a first generic small molecule applicant (ANDA applicant) reflects the relatively lighter burden of an ANDA filer. That is, the first successful ANDA applicant who makes a “Paragraph IV” certification that the reference drug holder’s patents were invalid or not infringed is entitled to only 180 days of market exclusivity as opposed to the eighteen months of exclusivity granted to an interchangeable FOB section (k) applicant. 21 U.S.C. § 355(j)(5)(B)(iv).

138. 35 U.S.C. § 271(a) (2006).

139. Generally, a patent provides at least twenty years of protection from the date of the earliest filed nonprovisional application to which the patent claims priority. 35 U.S.C. § 154(a). That patent term may be increased by means of a patent term adjustment (“PTA”), which is granted due to delays on the part of the Patent Office during prosecution. *Id.* § 154(b). In addition, a patent may be granted a patent term extension (“PTE”) for a limited period of the delay caused by the FDA regulatory approval process to compensate for time lost to seeking FDA approval. *Id.* § 156. This PTE is limited to a period of five years. *Id.*

140. As discussed *infra* Part VI, enactment of the America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011), which changes U.S. patent law such that an inventor who is “first to file” for patent protection has superior rights in the claimed invention, may push RBP innovators to file the patent applications earlier, or at least provisional patent applications, so as to preserve their rights.

141. See, e.g., PRICEWATERHOUSECOOPERS LLP, 2011 PATENT LITIGATION STUDY: PATENT LITIGATION TRENDS AS THE “AMERICA INVENTS ACT” BECOMES LAW (2011), available at <http://>

scope of the RBP innovator's patent protection, a FOB applicant may infringe on the RBP innovator's patent rights by attempting to develop a FOB.¹⁴² The BPCIA sets out a general framework for identifying patent disputes and penalizes incomplete disclosures of potential patent coverage.¹⁴³ This encourages early identification and resolution of such disputes.

In marked contrast to the manner in which patent disputes are identified and resolved in connection with the ANDA process for generic drugs, the BPCIA does not provide a public registry listing the patents that apply to particular RBPs.¹⁴⁴ An ANDA applicant can refer to the FDA's "Orange Book," which lists patents for products approved under an NDA.¹⁴⁵ An ANDA applicant is required to disclose information to the reference product holder only if the applicant is filing a "Paragraph IV" certification, under which the applicant challenges the scope, validity, or enforceability of the patent or patents listed in the Orange Book for the reference product.¹⁴⁶ The BPCIA, on the other hand, provides for a timed exchange of information, initiated by the FOB applicant, who must provide the RBP innovator with access to highly confidential manufacturing information.¹⁴⁷

Upon submitting a FOB application to the FDA, a FOB applicant has twenty days in which to provide the RBP innovator with confidential access to a copy of the FOB application and detailed information regarding the FOB applicant's manufacturing process.¹⁴⁸ Upon receipt of such confidential access, the RBP innovator has sixty days to produce to the FOB applicant a list of any patents, owned or exclusively licensed by the RBP innovator, which it believes covers the RBP, its manufacturing process, and/or its methods of use for which it re-

[/www.pwc.com/us/en/forensic-services/publications/assets/2011-patent-litigation-study.pdf](http://www.pwc.com/us/en/forensic-services/publications/assets/2011-patent-litigation-study.pdf).

142. Arguably, such attempts to develop a FOB are protected from patent infringement claims under the safe harbor provision, if conducted for the sole purpose of obtaining data reasonably related to the preparation of a submission for regulatory approval. *See* 35 U.S.C. § 271(e)(1).

143. 42 U.S.C. § 262(l) (2006 & Supp. IV 2011).

144. *Id.* § 262(l)(3).

145. ORANGE BOOK, *supra* note 82, at ADA1-ADA207.

146. 21 U.S.C. § 355(j)(2) (2006).

147. 42 U.S.C. § 262(l).

148. *Id.* § 262(l)(2). The confidential information is provided to the RBP innovator's outside counsel, one in-house counsel, and a representative of a patent exclusively licensed by the RBP innovator. *See id.* § 262(l)(1)(B)(ii)-(iii). Failure to provide the confidential information provides the RBP innovator the ability to file a declaratory judgment suit. *See id.* § 262(l)(9)(C).

ceived FDA marketing approval.¹⁴⁹ The FOB applicant then has sixty days following the receipt of said list to provide the RBP innovator with a list of the patents it believes covers the RBP, its manufacturing process, and/or its methods of use for which it received FDA marketing approval. It must also provide: (1) a representation that it will not market the FOB until the expiration of each of the RBP innovator's patents that it believes cover the RBP, its manufacture, or its use; (2) a detailed statement as to why the FOB and its use and manufacture do not infringe any of the RBP patents; and/or (3) a detailed statement as to why the RBP patents are not valid or are not enforceable.¹⁵⁰ The RBP innovator subsequently has sixty days to provide the factual and legal basis of infringement.¹⁵¹ Within fifteen days of the communications between the RBP innovator and FOB applicant, the parties must negotiate the patents to be litigated.¹⁵² If the parties agree, the RBP innovator has thirty days from the date of agreement to bring suit.¹⁵³ If there is no agreement, then the parties exchange a list of patents that each believes should be litigated.¹⁵⁴ The RBP innovator then has thirty days from the date of exchange to bring suit.¹⁵⁵ Failure of the RBP innovator to meet the statutory deadlines may preclude it from asserting its patents against the proposed FOB at issue or may limit the potential damages available.¹⁵⁶

As further discussed below, this process and the potential preclusive effect of choices, in terms of which patents to list and which to litigate, makes it vitally important—even imperative—for both the RBP innovator and the FOB manufacturer to be prepared with comprehensive and detailed information about patent coverage.

149. *Id.* § 262(l)(3)(A). Patents not included in the list, but that exist at that time, may not be asserted in litigation against that FOB applicant. *See* 35 U.S.C. § 271(e)(6)(C).

150. 42 U.S.C. § 262(l)(3)(B)(i)–(ii). The FOB applicant also must respond to any offer to license patents from the RBP innovator. *See id.* § 262(l)(3)(B)(iii).

151. *Id.* § 262(l)(3)(C).

152. *Id.* § 262(l)(4).

153. *Id.* § 262(l)(6)(A). The RBP innovator may add to the suit any newly issued or exclusively licensed patent upon proper notice to the FOB applicant. *Id.* § 262(l)(7).

154. *Id.* § 262(l)(5)(B).

155. *Id.* § 262(l)(6)(B).

156. *See* 35 U.S.C. § 271(e)(6)(A)–(B) (providing a reasonable royalty as the sole and exclusive remedy for infringement of patents for which the RBP innovator did not assert within thirty days); *see also* 42 U.S.C. § 262(l)(6). The language of the statute states that the sponsor “shall bring an action” within 30 days. *Id.* Some commentators have interpreted the statute as barring late assertions of patents by the RBP innovator if statutory deadlines are not met.

V. Food and Drug Administration Draft Guidance in Implementing a Tiered Approach to Follow-on Biologics Approval

In February 2012, the FDA issued three draft guidance documents designed to implement the BPCIA.¹⁵⁷ The guidance documents provide a stepwise approach to the demonstration of biosimilarity and likewise detail the FDA's review of proposed biosimilar FOBs. In addition, the documents provide an in-depth review of the general scientific principles used to determine biosimilarity.¹⁵⁸

While much of the guidance documents delve into specific scenarios and necessary tests to establish biosimilarity, the FDA generally discusses the importance of a direct comparison between the FOB and the reference product (i.e., the reference product is used in the same tests as the FOB).¹⁵⁹ The guidelines discuss a tiered approach under which an applicant would first adduce analytical studies which demonstrate that the biological product is highly similar in terms of structure: (1) primary amino acid sequence; (2) modification to amino acids; (3) higher order structure (i.e., protein folding); and (4) quaternary structure (i.e., interactions of subunits).¹⁶⁰ Animal studies will assess toxicity. Comparative human pharmacokinetic studies then will demonstrate that the FOB and the RBP act in the same manner in a human population. Finally, immunogenicity studies will show that the FOB does not create unanticipated and potentially harmful immune responses in patients.

The FDA does not provide product-class specific guidance on how to demonstrate bioequivalence. The guidance documents do encourage frequent interaction between the FDA and the proposed FOB developer ("sponsor") in order to negotiate and agree upon the testing necessary to demonstrate bioequivalence. Sponsors should meet early with FDA. At that time the sponsor can provide the FDA with a proposed plan for its development program, "manufacturing process information (including planned methodology and assay validation),

157. QUALITY CONSIDERATIONS, *supra* note 31; SCIENTIFIC CONSIDERATIONS, *supra* note 26; U.S. DEP'T OF HEALTH & HUMAN SERVS. ET AL, GUIDANCE FOR INDUSTRY ON BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009, DRAFT GUIDANCE (2012), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf> [hereinafter QUESTIONS AND ANSWERS].

158. QUALITY CONSIDERATIONS, *supra* note 31; SCIENTIFIC CONSIDERATIONS, *supra* note 26; QUESTIONS AND ANSWERS, *supra* note 157.

159. QUALITY CONSIDERATIONS, *supra* note 31, at 9.

160. SCIENTIFIC CONSIDERATIONS, *supra* note 31, at 7, 9–10.

and preliminary comparative analytical data with the reference product.”¹⁶¹ The FDA contemplates working with sponsors to evaluate that proposed plan and to frame the requirements for showing biosimilarity and interchangeability.

VI. Biologics and the America Invents Act

On September 16, 2011, President Obama signed into law AIA.¹⁶² Though the new patent law does not explicitly address biologics, it affects every area of innovation and patent protection. It makes sweeping changes to U.S. patent law attempting to harmonize it with international patent law. Perhaps the most significant change is the AIA’s incorporation of a “first to file” standard for patent protection—a departure from the “first to invent” standard previously applied.¹⁶³ Summarized below are some of the most significant changes to patent law implemented by the AIA and the manner in which those changes might affect patent practice relating to biologics.

A. Novelty, Obviousness, and the First to File System

To be patentable, an invention must be novel—it cannot have been previously described or used by others.¹⁶⁴ In addition, it must not be obvious in light of prior art already known.¹⁶⁵ Prior art encompasses written publications, such as patents and articles, as well as previous uses of the invention or something very similar to the invention.¹⁶⁶ For example, similar to the law prior to the AIA, an invention may be found to be unpatentable as obvious if components of the invention are disclosed in several different pieces of prior art (i.e., a previous patent and a published article), and it would have been routine to combine those components to create the claimed invention.

One of the most substantial changes implemented by the AIA is that both novelty and obviousness are determined as of the effective filing date of the patent application.¹⁶⁷ This departs from the previous

161. QUESTIONS AND ANSWERS, *supra* note 157, at 4.

162. Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011).

163. *See infra* Part VI.A.

164. 35 U.S.C. § 102 (2006).

165. *Id.* § 103.

166. *Id.* § 102 (defining disclosures that constitute prior art).

167. The effective filing date is the actual filing date or the filing date of the earliest application to which the patent or application is entitled to claim priority. § 3(b), 125 Stat. at 286–87 (amending 35 U.S.C. § 102(d)).

standard, which utilized the date of the invention.¹⁶⁸ This change builds consistency between U.S. and international patent law, where globally the individual or entity that is first to file for patent protection has priority (superior rights) over others with respect to the claimed invention.¹⁶⁹

The AIA does preserve the one-year grace period for disclosures made by the inventor, or an entity that obtained their information from the inventor, such that an inventor who files for patent protection in November 2011 is not barred by its publication of the invention in December 2010.¹⁷⁰ Disclosure of the invention or of information that makes the invention obvious by a third party that did not receive the information from the inventor invalidates prior art if it occurs at any time prior to the inventor's filing.¹⁷¹

Changing from the first to invent to a first to file as a basis for priority¹⁷² is intended to provide greater certainty for inventors that their patent will not be invalidated by someone who claims an earlier date of invention.¹⁷³ This change in the law, however, is likely to increase pressure on inventors of biologics. A biologic inventor will want to file for patent protection as soon as possible, to preserve exclusive rights to their innovation. It may take a significant amount of time, however, to fully and completely characterize an innovative biologic or particular formulation for administering a biologic to patients. It can be argued that a first to file system will put additional pressure on companies seeking patent protection for biologics. Also, as discussed in more detail herein, the challenges of scaling-up production, preparing formulations that exhibit the desired stability both *in vitro* and *in vivo*, and designing molecules that exhibit the desired pharmacokinetics when administered to a subject, can be more complicated and time-consuming for biologics than for small molecule drugs. Thus, it can be envisioned that the increased importance of early filing under the AIA may impose a higher hurdle on a biologic inventor than did the pre-AIA criterion of a "first to invent" patent system on a biologic inventor.

168. § 3(b)-(c), 125 Stat. at 285-87 (amending 35 U.S.C. §§ 102-103).

169. See § 3(o), 125 Stat. at 293 (providing a sense of Congress' rationale for the AIA).

170. § 3(b), 125 Stat. at 285-87 (amending 35 U.S.C. § 102).

171. *Id.*

172. The first to file system will be implemented eighteen months after enactment of the Act. § 3(e)(3), 125 Stat. at 288.

173. See § 3(o), 125 Stat. 293 (providing a sense of Congress' rationale for the AIA).

B. Written Description and Enablement Requirements

Notwithstanding the new focus on the date of filing for patent protection, the AIA does not change the burdens placed on an inventor by the “written description” and “enablement” requirements under the U.S. patent law. To satisfy these requirements, an inventor must provide not only a comprehensive, definite, and detailed description of her invention, but also must provide sufficient information to enable a “person skilled in the [relevant] art . . . to make and use the [invention].”¹⁷⁴

To satisfy the written description and enablement requirements,¹⁷⁵ an inventor is required to provide a comprehensive description of the compound for which patent protection is sought. This can be particularly challenging for the biologics’ inventor. While it may be fairly straightforward to provide a description of a single biologic molecule (i.e., a protein therapeutic or monoclonal antibody) and to provide initial studies showing efficacy for certain indications, it may take several years to explore what changes can be made to the molecule to improve or preserve function. Similarly, characterizing the complete spectrum of diseases for which the biologic may have therapeutic benefits, developing a stable formulation, and developing large scale culture conditions may take several years. Obtaining patent protection is desirable for a RBP innovator in order to protect the investment of work spent determining all variations of a biologic (to identify and describe sequencing and structural variations that have pharmaceutical utility), all indications, formulations, and culture conditions by obtaining patent protection. If the biologic is not adequately protected by patent, then many if not all of these aspects are potential routes for a design-around (a FOB that is just different enough to avoid the RBP’s patent protection).

In some cases, the reference company might not choose to provide any public disclosure about the biologic until a good portion of this characterization has been accomplished. Or, in some cases, a company may choose to use provisional patent application to protect the biologic.¹⁷⁶ For example, a provisional application may be filed providing an initial disclosure of at least some aspects such as the chemical composition, early animal testing, and data relating to therapeutic indications for a biologic. If after one year, the research has not

174. 35 U.S.C. § 112 (2006).

175. *Id.*

176. *Id.* § 119(e).

progressed to the point where the written description can encompass claims for desired embodiments, such as, but not limited to, a relevant number of bioequivalent molecules, the most important therapeutic indications, formulations, and/or production of the biologic, that provisional application can be abandoned. If additional experimental results become available during the pendency of the first provisional filing, then additional provisional applications containing the new data may be filed. Subsequently, these applications can be abandoned and refiled as necessary during the development and characterization process before converting the provisional application(s) to a U.S. non-provisional or PCT international patent application.¹⁷⁷

Alternatively, the developer of a biologic may choose to file separate patent applications for the various improvements to the initial product. For example, a first patent application may cover the compound and the initial therapeutic indications; a second patent application may cover additional therapeutic applications; and a third patent application may cover the formulation.

These various filing strategies are, however, very similar to filing strategies required under pre-AIA law.

C. New Proceedings for Challenging or Reviewing Pending and Issued Patents

The AIA also makes sweeping changes to procedures available for attacking or reviewing patent applications and issued patents. Prior to the AIA, proceedings available for challenging patent applications or patents included *ex parte* citation of prior art in an application,¹⁷⁸ or *ex parte* reexamination proceedings,¹⁷⁹ both of which are still available under the patent statute. The AIA replaces *inter partes* reexamination proceedings¹⁸⁰ with *inter partes* review,¹⁸¹ discussed in more detail below.

These new avenues for critical assessment of patents and pending applications should improve the quality of issued U.S. patents. The new procedures do not mitigate the burdens on a biologic patent applicant created by the juxtaposition of the need to fully characterize

177. *Id.* § 119(e)(1).

178. *Id.* § 301 (providing for citation of prior art to the USPTO).

179. *Id.* §§ 302–307 (providing for citation of prior art to the USPTO and *ex parte* reexamination).

180. *Id.* §§ 311–318 (providing for *inter partes* reexamination).

181. Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 6(a), 125 Stat. 284, 299 (2011) (amending the rules for *inter partes* review).

biologic compounds with the new urgency to file as soon as possible. The FDA does provide a RBP innovator (or, in some circumstances, a third party such as an aspiring FOB applicant) with procedures for challenging patent applications or patents that are believed to be based on the invention of someone other than the applicant, or are otherwise invalid for lack of novelty, or for failure sufficiently to describe or teach the claimed invention. A biologic inventor who has been “scooped” by an earlier patent application filing may challenge the filer’s rights. An applicant who filed too early—before knowing enough about the claimed invention to satisfy written description requirements—may also lose priority if the patent is ruled invalid.

1. Derivation Proceedings

The AIA’s first to file system is qualified by the rule that a patent to a claimed invention will not be valid if the invention is “derived” from another. The AIA provides for derivation proceedings,¹⁸² which will replace current interference practice.¹⁸³ Such derivation proceedings must be filed within one year of publication of the petitioner’s claim to the same or substantially the same invention as the earlier filed, allegedly derived invention.¹⁸⁴ The Director of the Patent Office then institutes derivation proceedings if the required standards are met.¹⁸⁵ The AIA also provides for a civil derivation proceeding under 35 U.S.C. § 135, which may be filed later—within one year after the issuance of the patent on the allegedly derived invention.¹⁸⁶

Given the potential time lag between biologic innovation and the ability fully to describe and claim a biologic invention with specificity sufficient to support a patent application, the derivation proceeding is a potential “fall back” for the biologic innovator who believes that another has filed for patent protection for the invention. It will be important for companies producing biologics to diligently monitor

182. § 3(h), 125 Stat. at 288 (amending 35 U.S.C. § 291). The rules governing derivation proceedings come into effect eighteen months after enactment of the AIA. § 3(k), 125 Stat. at 291.

183. Under the current patent laws, an interference can be declared by the USPTO and/or a party where the claims of two applications and/or an application and an issued patent are the same. 35 U.S.C. § 135. Such proceedings provide a forum to determine whom first invented the claimed invention; the first to invent is awarded priority and that party’s patent will issue.

184. § 3(h), 125 Stat. at 288.

185. As of the writing of this Article, draft rules relating to derivation practice have been provided by the USPTO for public comment. *See* USPTO, <http://www.uspto.gov> (last visited May 10, 2012).

186. § 3(h), 125 Stat. at 288.

prosecution of potentially relevant patent applications by competitors in order to determine whether those applications include “derived” claims.

2. Post-Grant Review and *Inter Partes* Review

One of the most important changes implemented by the AIA is the post-grant review proceeding.¹⁸⁷ These proceedings are conducted by the Patent Trial and Appeal Board and provide a forum much like the opposition proceedings, which occur in Europe. The post-grant review may be filed on the basis of alleged prior art that anticipates the invention or renders it obvious, or on the basis that the specification does not provide adequate written description or enablement for the invention as claimed.¹⁸⁸ The post-grant review must be filed within nine months after the patent is granted.¹⁸⁹

Inter partes review proceedings¹⁹⁰ are available after a Post-Grant Review Proceeding is terminated (or nine months after a patent is granted, whichever is later). *Inter partes* review may be based “only on a ground that could be raised under section 102 or 103 [anticipation or obviousness] and only on the basis of prior art consisting of patents or printed publications.”¹⁹¹

3. Pre-Issuance Submissions

The AIA also provides for a new procedure under which any party may submit prior art to the PTO so that the patent examiner can consider such information in its determination as to whether a patent should be issued.¹⁹² Such art must be submitted within certain time frames during prosecution of the application.¹⁹³ A potential chal-

187. § 6(d), 125 Stat. at 305 (amending post grant review proceedings at 35 U.S.C. §§ 321–329). The post-grant review proceeding will take effect one year after enactment of the AIA on any patent or application with an effective date on or before the one-year after enactment date. § 6(f)(2)(A), 125 Stat. at 311.

188. § 6(d), 125 Stat. at 306 (noting that post grant review may be initiated on any ground that could be raised under paragraph (2) or (3) of section 282(b), which relates to invalidity of the patent or any claim).

189. *Id.*

190. § 6(a), 125 Stat. at 299 (amending 35 U.S.C. §§ 311–319 and renaming Chapter 31 from “optional *inter partes* reexamination procedures” to “*inter partes* review”).

191. *Id.* (amending 35 U.S.C. § 311(b)).

192. § 8(a), 125 Stat. at 315 (codifying preissuance submissions by third parties at 35 U.S.C. § 122(e)).

193. The submission is to be filed along with a statement of relevance of the art submitted, and is to be filed by the earlier of: (1) a Notice of Allowance; or (2) the later of six months after publication or the date of a first substantive rejection of the claims by the USPTO. *Id.*

lenger thus must diligently monitor prosecution of pending applications. It should also carefully consider whether the prior art at issue might be more effectively presented in civil invalidity proceedings. Once prior art is submitted during prosecution, a later civil challenge on the basis of that art (if the patent issues) is significantly weaker than if the prior art had not been before the Patent Office.

4. Supplemental Examination Available to Patent Applicant

The AIA's new supplemental examination procedure provides a means by which applicants may submit additional information to the PTO after issuance of their patent.¹⁹⁴ Such disclosures include publications previously not disclosed, or potential mischaracterizations of a claimed invention made during prosecution of the application, or other disclosures, that during a litigation proceeding could be found to render a patent unenforceable due to inequitable conduct. The AIA provides that "a patent shall not be held unenforceable on the basis of conduct relating to information that was not considered, was inadequately considered, or was incorrect in a prior examination of the patent if the information was considered, reconsidered, or corrected during a supplemental examination of the patent."¹⁹⁵ The ability to request supplemental examination may reduce the number of inequitable conduct challenges in litigation by providing applicants the opportunity to correct potential omissions or mischaracterizations that may have occurred during prosecution.

D. Effect of New Review Proceedings on Patent Validity Litigation

The new post grant review and *inter partes* review proceedings pursuant to the AIA will be much more like civil patent infringement litigation than PTO reexamination proceedings under the previous patent law. The AIA proceedings can be filed by any party that is not the owner of the patent and are conducted independently of the patent examiner.¹⁹⁶ If any of these new post-publication proceedings under the AIA are filed before civil patent litigation, the civil litigation will be stayed, and the Patent Office's decision may ultimately be bind-

194. § 12, 125 Stat. at 325 (codifying supplemental examination proceedings at 35 U.S.C. § 257).

195. *Id.*

196. § 6(d), 125 Stat. at 305 (amending post-grant review proceedings under 35 U.S.C. §§ 321–329); § 6(a), 125 Stat. at 299 (recodifying "*inter partes* reexamination" as "*inter partes* review proceedings" under 35 U.S.C. §§ 311–319).

ing on civil litigants.¹⁹⁷ Conversely, if a civil court case challenging patent validity is filed first, none of the new post-publication proceedings are available.¹⁹⁸ The new review proceedings thus provide a new forum for challenging a competitor's patent, but require a high level of preparedness and diligence in monitoring patent applications and patents.

E. Additional Aspects of the America Invents Act Relating to Patent Litigation

The AIA also redefines several defenses to patent infringement claims. In conjunction with the new patent review procedures described above, these changes heighten the importance of preparedness and early attention to strategy—both for a reference biologic inventor and for a FOB applicant seeking to design around or to invalidate the inventor's patent protection. Among the changes that will affect planning for reference biologic innovators and aspiring FOB applicants are:

- Elimination of the “best mode” defense: Past law provided an invalidity defense for failure to disclose the best mode of practicing an invention known to the inventor at the time of filing for patent protection.¹⁹⁹ An inventor is still required to describe, in the patent itself, the best manner of making a claimed compound or device, or the best way to practice a claimed method. Now, however, an inventor's failure to disclose that “best mode” is not a defense to patent infringement.²⁰⁰ The AIA thus renders a reference biologic innovator's patent less vulnerable to an invalidity attack in infringement litigation against a FOB applicant;
- Enlargement of the “prior use” defense: In the past, a patent claiming a method, i.e., for formulating a biologic, could be attacked as invalid on the basis a commercial use within the United States at least one year before the patent's effective filing date.²⁰¹ The AIA provides that this “prior use” defense is no longer restricted to method claims, but can be used to in-

197. § 6(a), 125 Stat. at 299; § 6(d), 125 Stat. at 305.

198. Counterclaims of invalidity are not subject to this restriction. § 6(a), 125 Stat. at 299; § 6(d), 125 Stat. at 305.

199. 35 U.S.C. § 112 (2006).

200. § 15(a), 125 Stat. at 328 (amending 35 U.S.C. § 282(3) and specifically stating that failure to disclose the best mode will not be grounds for cancellation).

201. 35 U.S.C. § 273(b).

validate claims for compositions or devices as well.²⁰² The AIA also now includes commercial uses outside the United States.²⁰³ Development and use of biologics outside the United States now may constitute a “prior use” defense to patent infringement allegations; and

- Expansion of the scope of potentially invalidating prior art: Past law provided that a patent was invalid on proof that the invention was known or used in the United States, or described in a patent or printed publication, in the United States, more than one year before the effective filing date of the patent.²⁰⁴ The AIA expands invalidity defenses under section 102 to include defenses based on prior knowledge, use, or description in a patent or printed publication anywhere in the world.²⁰⁵ This provision makes it easier for a FOB applicant to attack a reference biologic innovator’s patent. It also highlights the importance of conducting thorough and broad prior art searches, both for the patentee and an accused infringer.

VII. Strategies for Players in the Biologics Market: How Best to Negotiate the New Legal Landscape

The new law and regulatory framework for reference biologics, FOBs, and patent law, urge that both a RBP innovator and a FOB applicant take several steps. These include developing strategies for: (1) addressing the FDA application pathway, (2) the disclosure requirements, (3) patent prosecution and monitoring, (4) patent portfolio management, and (5) patent enforcement to be positioned for marketplace success under the new law. The new law heightens the importance for RBP innovators and FOB applicants to be armed with complete information (or as complete information as feasibly can be obtained) about prior art, pending U.S. and foreign patent applications, issued patents, and development and uses of biologic products both in and outside the United States. The following sections describe strategies for both RBPs seeking to protect and maximize gain from their innovation and for FOBs seeking to carve out a piece of the biologics market to protect their innovations and processes.

202. § 5(a), 125 Stat. at 297 (amending 35 U.S.C. § 273 to include machines, manufactures, and compositions of matter).

203. § 3(b), 125 Stat. at 285 (amending 35 U.S.C. § 102).

204. 35 U.S.C. § 102.

205. § 3(b)(1), 125 Stat. at 285 (amending 35 U.S.C. § 102).

A. Strategies for a Reference Biologic Product Innovator

1. Review Patent Portfolio

To best position itself in view of the new approval pathway, a RBP innovator should carefully review its patent portfolio to determine which patents and patent applications could cover the RBP it intends to market. Once identified the RBP innovator should assess the potential strengths and weaknesses of the identified patents and applications to best protect its product while asserting patent infringement claims or countering allegations of invalidity or unenforceability. Once an application is filed with the FDA by a FOB and notice is provided to the RBP innovator of the application, the RBP innovator only has sixty days to respond to the notice by requesting additional information and by providing a list of patents that it believes the FOB applicant may infringe if it makes, uses, sells, or imports the FOB in the United States. Early review of its patent portfolio is critical to allow a RBP innovator properly to respond under the tight deadlines imposed by the BPCIA, focusing on the patents that it believes are infringed by each FOB applicant, the patents it is willing to license to each FOB applicant, and the arguments it will make against any assertions of non-infringement, unenforceability, and invalidity. The RBP innovator must be prepared with information to make decisions about which of its patents are strong enough to assert against each FOB applicant.

The RBP innovator also should keep continuation applications pending, if possible, for each of its key patents relating to its product and the methods of making and using the product. This enables it to maintain options for pursuing additional claims or perhaps a continuation-in-part application as needed to cover follow-on products as they are developed. Continuation applications provide the RBP innovator an opportunity to continue to claim additional subject matter that was disclosed, but not claimed in, the issued patents.²⁰⁶ By keeping continuation applications pending, the RBP innovator may prevent FOB applicants from “designing around” the issued claims. In addition, the RBP innovator should consider whether a narrowing reissue or reexamination process would be effective to solidify its rights in view of relevant prior art. If in analyzing its patent portfolio, the RBP innovator identifies certain patent claims that arguably are overly broad and are likely to be challenged by the FOB applicant based on prior art references, the RBP innovator can preempt such attacks by seeking to

206. 35 U.S.C. § 120.

amend the claims through a narrowing reissue or reexamination process to a more appropriate claim scope.

2. Expand Patent Protection for Broader Exclusivity

The RBP innovator should consider whether it can preempt potential competition from a FOB applicant that designs molecules which fall outside the RBP innovator's patent claims, but nonetheless have substantially the same therapeutic utility by considering whether to file patent applications for such "design-around" molecules. Some of those molecules may be new chemical entities with a different amino acid sequence than the RBP. In this manner, the RBP innovator can strengthen its patent position relative to the FOB developer while also establishing a new patent term of twenty years for the design around molecules.

Some of the new molecules may act as "biobetters" with enhanced biological or therapeutic efficacy relative to the reference product. A RBP innovator with a therapeutic protein product may file new patent applications disclosing the amino acid sequence of therapeutic proteins with conservative amino acid substitutions at specific amino acid residues (such as alanine for leucine), if such substitutions result in enhanced efficacy. In another example, the RBP innovator may substitute asparagine or threonine amino acid residues at selected positions in the protein to facilitate single or multiple glycosylations of the protein, thereby prolonging the half-life of the therapeutic protein or possibly enhancing receptor binding. This results in a molecule with enhanced biological activity—a biobetter. Once a patent application for a biobetter publishes, the publication acts as a novelty-destroying event for a potential FOB developer pursuing the same protein. Alternatively, if the RBP innovator makes a strategic decision not to pursue patents on such proteins because it does not want to commit to the research and development expense of developing design around proteins, the RBP innovator may decide to publish an article. This has the potential of affecting the proposed patent application's novelty and perhaps rendering its claims (and the claims of other parties) obvious.

3. Identify the Competition and Potential Follow-on Biologic Applicants

The RBP innovator should know its competition by identifying, investigating, and monitoring: potential FOB applicants, their commercial activities, regulatory filings, issued patents, published patent

applications, and new partnerships and joint ventures with other companies.

Routinely monitoring the published patent applications and issued patents of competitors enables a RBP innovator to gain insight into the potential FOB applicants' patent portfolios. This approach provides several advantages to the RBP innovator. For example, the RBP innovator may have a superior insight into the prior art, having already prosecuted its own patent applications. The RBP innovator may decide to send relevant prior art to the potential FOB applicant company and its patent counsel in the United States, or perhaps directly to a Patent Office, thereby slowing patent prosecution or perhaps destroying patentability of some claims.

As discussed above the AIA provides several new routes for such submissions. An applicant should consider making its submission of relevant art with comments to focus the patent examiner. Further, if material prior art sent to a potential FOB applicant or its patent counsel is not disclosed to the USPTO the FOB developer and its patent counsel may be subject to charges of inequitable conduct and patent invalidity.²⁰⁷ This could seriously impede a FOB applicant that may not have the resources to fight such a battle. Further, the RBP innovator could decide to oppose an allowed patent of a FOB developer in Europe or use the new post grant review procedures in the United States. By performing such patent surveillance on competitors who may become FOB applicants, the RBP innovator can achieve tactical advantages and be better prepared to respond when a FOB application is filed.

B. Strategies for Follow-on Biologic Developers

1. Familiarity with Swift Biologics Price Control and Innovation Act Pathway Timing and Costs

FOB developers—potential FOB applicants—are motivated to be the first to file a FOB application because of the potential for significant profits and limited exclusivity (for a first “interchangeable” FOB). However, these companies must prepare for significant upfront costs of conducting patent due diligence on the RBP innovator and preparing arguments of patent invalidity for the RBP innovator's patents. The potential FOB applicant must also prepare for the costs associated with the defense of patent infringement litigation. A FOB developer also must be familiar with the requirements for a FOB ap-

207. 37 C.F.R. § 1.56 (2011); 37 C.F.R. pt. 11.

plication, which, as discussed above, are far more stringent and extensive than those applied to generic drugs.

2. Due Diligence on the Reference Biologic Product Innovator's Patents

Because there is no Orange Book equivalent that a potential FOB applicant can consult to determine what patents protect the RBP and the methods of making it, the FOB developer must perform its own due diligence on the RBP to make this determination and to identify the relevant patents' expiration dates. Due to the short response turn-around time after the RBP innovator provides a listing of patents believed to cover the FOB, an applicant should prepare an assessment of the validity and enforceability of any RBP innovator patents that it determines could protect the RBP before filing its FOB application. Such diligence investigation should include a review of the remaining patent terms, the scope of the issued claims, the arguments made by the RBP innovator during prosecution of the patent application that might lead to estoppel, related pending and published applications that may protect the RBP, and whether all required maintenance fees have been paid. It is also important that the FOB applicant determine whether any licenses are necessary from a third party in order to market its FOB.

The FOB developer should consider commissioning an invalidity search and a non-infringement and invalidity opinion letter from a patent attorney for the claims of the RBP innovator's patents covering the RBP. If resources are limited, the potential FOB applicant must perform its own search for prior art, arming itself with knowledge to decide whether there are viable arguments with respect to non-infringement, validity, or unenforceability of the RBP innovator's patents. A FOB applicant must prepare for the accelerated litigation schedule triggered by the submission of a FOB application. If it is not possible to make valid arguments against the RBP innovator patents, then the FOB applicant must wait to market its FOB until after the RBP innovator's patents expire.

If the FOB developer discovers invalidating prior art, it will be better prepared to make arguments of patent invalidity when the RBP innovator asserts its patents against the FOB. The FOB applicant also should consider whether to provide this prior art anonymously with statements concerning its materiality to the USPTO for consideration. The FOB applicant should also consider whether to file a request for reexamination of the RBP innovator's patents, using prior art patents

or printed publications, which have bearing on patentability of the relevant claims. If the RBP innovator's patent is within nine months of grant, the FOB applicant should consider an *inter partes* review procedure as an alternative.²⁰⁸

3. Review Intellectual Property Portfolio

The FOB applicant should carefully review its own patent portfolio to ensure that it has adequately protected its proprietary methods of manufacturing the FOB because the BPCIA requires that a FOB applicant's manufacturing methods be revealed to the RBP innovator. This warrants serious consideration because the BPCIA appears to mandate extensive disclosures of what would otherwise be considered highly sensitive and confidential trade secrets. Assurances of confidentiality may not provide adequate protection of a FOB developer's core business. The potential FOB applicant should also consider whether there is room to maneuver and design around the RBP innovator's patents.

4. Seek Patent Protection for New Molecules or Methods of Manufacture

If the FOB applicant is precluded from seeking patent protection for its FOB as a composition of matter because it falls within the claims of the RBP innovator's patent, the FOB developer should consider ways to design around the claims of the RBP innovator's patent. If the claims of the RBP innovator's patent are broader than the amino acid sequence of the RBP protein, then there may not be much room to design around the claims to create a new protein that may act as a biobetter. This is because the new protein also may fall within the scope of the patent claims. The FOB developer also should consider whether to file patent applications on its own methods of manufacturing the FOB or attempt to maintain these methods as a trade secret, especially in view of the disclosure requirement to the RBP innovator described above.²⁰⁹

If the RBP innovator's patent claims protect a few conservative amino acid substitutions of the reference product protein but not the substitution of amino acid residues with arginine, threonine, serine, or tyrosine for post-translational modifications, such as glycosylation or phosphorylation, then the FOB applicant should decide whether to

208. See *supra* Part VI.C (discussing the AIA's provisions for such review).

209. See *supra* Part IV.E.

create these molecules and examine their biological activity and toxicity through research and development. In this case, the FOB applicant may want to quickly file a provisional patent application covering these molecules that may be new chemical entities. Subsequent conversion of that patent application could eventually provide twenty years of patent protection. Subsequent research and development could demonstrate that these molecules may prove to have a greater biological activity and lower toxicity. In such an instance, the molecules could be deemed to be biobetters. As such, these molecules may be considered new molecules, which would be the subject of a new biologics license application rather than a FOB application.

C. Hypothetical

This section provides hypothetical examples of both the perspectives of a RBP company and of a FOB company in terms of specific biologics and patent strategy pursuant to the BPCIA and the AIA.

Adipolyse Pharmaceutical Company (“Adipolyse”) is a reference product company with a reference product called liposin, a peptide of twelve amino acids which functions to metabolize fat (lipolysis) and to reduce weight. The amino acid sequence of liposin is: Alanine – Leucine – Aspartic acid – Alanine – Tyrosine – Histidine – Glutamic acid – Proline – Leucine – Valine – Aspartic acid – Valine. This sequence is abbreviated as follows, wherein each amino acid residue is numbered from 1 at the N-terminus (the amino terminus, in this case alanine) to 12 at the C-terminus (Carboxy terminus, in this case valine) of the peptide (SEQ ID NO:1):

1	2	3	4	5	6	7	8	9	10	11	12
Ala	–Leu	–Asp	–Ala	–Tyr	–His	–Glu	–Pro	–Leu	–Val	–Asp	–Val

Adipolyse has a patent claiming the liposin peptide sequence, which expires in 2014. Adipolyse also holds patents for therapeutic methods of administering liposin for weight reduction. Adipolyse does not have patent protection for the method of making liposin as liposin is synthesized using the known method of solid phase synthesis. The FDA approved liposin to treat obesity. In view of the exploding epidemic of obesity in the United States and Europe, and the associated risks of diabetes, cardiovascular disease, and musculoskeletal disorders, Adipolyse has a billion dollar market.

Adipolyse's issued patent protects the liposin peptide sequence shown above, as well as a slightly different sequence (SEQ ID NO:2):

1	2	3	4	5	6	7	8	9	10	11	12
Ala	-Ala*	-Asp	-Ala	-Tyr	-His	-Glu	-Pro	-Leu	-Val	-Asp	-Val

SEQ ID NO:2 has an alanine (Ala) for leucine (Leu) substitution at position 2. Adipolyse could not obtain broader patent protection for the composition patent as the patent examiner would not budge—only allowing the two sequences that Adipolyse demonstrated were effective in metabolizing fat. Adipolyse is considering a biosimilars application to the FDA for SEQ ID NO:2 and does not expect any problems due to the conservative amino acid substitution at position 2.

Although Adipolyse believes the validity of its composition patent, it has a continuation application pending and is considering filing a continuation-in-part application to cover slightly different sequences with modifications at positions 1, 9, 10, and 11. It aims to prevent patent protections for possible design around molecules by biosimilar applicant or other competitor.

Slim N Fit is a small company with limited resources. Slim N Fit's business plan is to gain market share in the field of diabetes by developing peptides that increase metabolism, reduce body weight, and increase the amount of brown fat which is more metabolically active than other fat. Slim N Fit is aware of Adipolyse's patent covering SEQ ID NOs: 1 and 2, and it employs a team of peptide chemists and molecular biologists to develop efficient methods of making these sequences in bacteria at a fraction of the cost of the solid phase synthesis techniques employed by Adipolyse. Slim N Fit also conducted due diligence on Adipolyse and found prior art published in Japan two years before the priority date of Adipolyse's patent that Slim N Fit believes would invalidate Adipolyse's patent.

Slim N Fit decided to file biosimilar applications with the FDA for both SEQ ID NOs: 1 and 2, although it decided to first file a patent application on its method of making these sequences. During research and development, Slim N Fit made additional sequences that are variations of SEQ ID NOs: 1 and 2. These are SEQ ID NOs: 3, 4, and 5:

SEQ ID NO:3

1	2	3	4	5	6	7	8	9	10	11	12
Ala	-Leu	-Asp	-Ala	-Tyr	-His	-Glu	-Pro	-Leu	-Val	-Asn*	-Val

SEQ ID NO: 4

1	2	3	4	5	6	7	8	9	10	11	12
Ala	-Leu	-Asn*	-Ala	-Tyr	-His	-Glu	-Pro	-Leu	-Val	-Asp	-Val

SEQ ID NO:5

1	2	3	4	5	6	7	8	9	10	11	12
Ala	-Leu	-Asn*	-Ala	-Tyr	-His	-Glu	-Pro	-Leu	-Val	-Asn*	-Val

Slim N Fit discovered that substitution of an asparagine (Asn) for aspartic acid (Asp) at position 3 and/or 11 to create a glycosylation site permitted one or more sugar residues to be added to the molecule during biosynthesis. These molecules containing sugars were fifty percent more biologically active to burn fat, were resistant to being degraded in the blood, and were able to convert white fat cells to brown fat cells.

In addition to filing a patent application claiming methods to manufacture SEQ ID NOs: 1, 2, 3, 4, and 5, Slim N Fit also filed a provisional application to protect the compositions of SEQ ID NOs: 3, 4, and 5. Slim N Fit believes SEQ ID NOs: 3, 4, and 5 are new compositions of matter, which are biobetters compared to SEQ ID NOs: 1 and 2. It also believes that they may obtain twenty years of patent protection, thereby gaining market share and avoiding Adipolyse's patent. However, since Slim N Fit's resources are limited, it plans to try to piggyback on the safety and efficacy data in Adipolyse's FDA application to see if it can push SEQ ID NOs: 3, 4, and 5 through regulatory approval as biosimilars to SEQ ID NOs: 1 and 2. During that process, Slim N Fit is seeking a strategic partnership through a license with a competitor of Adipolyse to develop clinical data for a regulatory submission. In this manner it will be prepared to file a BLA if the FDA does not accept SEQ ID NOs: 3, 4, and 5 as biosimilars to SEQ ID NOs: 1 and 2.

Conclusion

In view of the new law and the recently issued FDA guidance,²¹⁰ both innovator companies, and companies making FOBs must carefully plan patent strategy, while addressing the nuances of regulatory

210. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001-7003, 124 Stat. 119, 804-21 (2010); Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011); SCIENTIFIC CONSIDERATIONS, *supra* note 26.

approval requirements. The intersection of the new patent law and the BPCIA's provisions for FOBs is an emerging area of the law that will undoubtedly be tested and defined in the federal courts, as RBP and FOB companies seek to protect their innovations and return on investment, even as there is increasing societal pressure to hasten delivery of therapeutic biologics at lower cost to patients and the health care system.