
CASE NOTES AND COMMENTS

Therapeutic Monoclonal Antibodies: The Dilemma of Delivering Affordable Biologics to Patients While Continuing to Incentivize Innovation

I. INTRODUCTION

In October 2008, Eli Lilly agreed to acquire ImClone for six and a half billion dollars.¹ Eli Lilly outbid Bristol-Myers Squibb² and “cleaned out the cash coffers” to seal the deal.³ The company did not pay billions of dollars for a huge, diverse portfolio of established drugs. Rather, the transaction was driven by a single blockbuster, Erbitux,⁴ and three drugs still in clinical trials awaiting FDA approval.⁵ ImClone’s three pipeline drugs, while a significant financial risk,⁶ are likely worth the gamble.⁷ Erbitux and the other three treatments are monoclonal antibodies, highly complex molecules derived from living cells.⁸ In addition to their value as successful treatments, the antibody drugs are valuable because they are inherently difficult for competitors to copy.⁹

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1. Shirley S. Wang, *Lilly Agrees to Acquire ImClone for \$6.5 Billion*, WALL ST. J., Oct. 7, 2008, at B3.
 2. See Lawrence C. Strauss, *Browsing in the Biotech Aisle*, BARRON’S, Aug. 18, 2008, at 44 (reporting Bristol-Myers Squibb bid \$4.5 billion for ImClone).
 3. Tom Murphy, *Lilly, Bristol-Myers Post Solid 3Q Sales Growth*, ASSOCIATED PRESS, Oct. 23, 2008, available at <http://www.thefreelibrary.com/Lilly%2c+Bristol-Myers+post+solid+3Q+sales+growth-a01611680719> (quoting Erik Gordon, head of biomedical industry programs at Stevens Institute of Technology).
 4. Erbitux, commonly known as cetuximab, treats advanced colorectal cancer. FDA, Cetuximab (Erbitux) and Panitumumab (Vectibix), <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm172905.htm> (last visited May 26, 2010). ImClone developed Erbitux but licenses the domestic marketing rights to Bristol-Myers Squibb and the foreign rights to Merck of Germany. Andrew Pollack, *Eli Lilly Agrees to Buy ImClone Systems for \$6.5 Billion*, N.Y. TIMES, Oct. 7, 2008, at B7.
 5. See Wang, *supra* note 1 (listing 1121B, A12, and 11F8 as pipeline drugs).
 6. Catherine J. Arnold et al., *Eli Lilly’s ImClone Deal Adds Risk*, BARRON’S, Oct. 10, 2008, <http://online.barrons.com/article/SB122358964458520741.html>.
 7. See Catherine Arnst, *Why All the ImClone Interest? Its Pipeline*, BLOOMBERG BUSINESSWEEK, Oct. 3, 2008, http://www.businessweek.com/technology/content/oct2008/tc2008102_149704.htm (noting that buying pipeline is more efficient than starting from scratch and ImClone has one of strongest oncology pipelines in industry).
 8. Wang, *supra* note 1.
 9. See *infra* Part II.A.3 for a discussion of molecule design and manufacturing challenges.

Besides Eli Lilly, other pharmaceutical titans are similarly hustling to settle acquisition deals to secure promising biologic drugs.¹⁰ When asked about the general shift of pharmaceutical companies' resources "into biologics, such as therapeutic antibodies, as opposed to small-molecule drugs," the Research and Development ("R&D") Chairman at GlaxoSmithKline replied that "[t]here is a scientific driver and a business driver. . . . Strategically, I do not think that biopharmaceuticals will experience the same cliff when the patent expires as new chemical entities. It is extremely complex to make an identical biopharmaceutical."¹¹ Simply put, "big pharma" is banking on complex biologics to provide a portfolio resistant to generic competition.¹²

Small-molecule pharmaceuticals embody the traditional notion of therapeutic drugs: chemically synthesized pills composed of a homogenous collection of molecules.¹³ Biologics are a separate class of drugs distinguished by their biological origin.¹⁴ Rather than being synthesized in test tubes using chemical building blocks, biologics are produced by living cells using life's building blocks: sugars, proteins, and nucleic acids.¹⁵ Biologics are generally more complex than small-molecule drugs and are more difficult to characterize.¹⁶ Pharmacies dispense most prescription small-molecule drugs as pills, in quantities lasting days or weeks.¹⁷ In contrast, a health care provider must administer most biologics intravenously on a dose-by-dose basis.¹⁸ Currently, a legislative pathway exists for copycat small-molecule pharmaceuticals to obtain FDA approval.¹⁹ Such copycats are known as generics. An analogous

10. In July 2009 Bristol-Myers Squibb acquired Medarex. Jennifer Boggs, *Attention Shoppers: Antibody Prizes Not Limited to Medarex*, BIOWORLD, July 24, 2009, http://www.bioworld.com/servlet/com.accumedia.web.Dispatcher?next=bioworldHeadlines_article&forceid=51567. In April 2007, AstraZeneca acquired MedImmune. Andrew Pollack, *AstraZeneca Acquires a Biotech Company*, N.Y. TIMES, Apr. 24, 2007, at C3.

11. Heidi Ledford, *The Future of Pharma: GSK's Research Leaders Answer Nature's Questions About Where Their Company—and Their Industry—Is Headed*, NATURE.COM, Oct. 9, 2008, <http://www.nature.com/news/2008/081009/full/news.2008.1161.html> (interviewing Moncef Slaoui, twenty-year veteran of GSK and current Chairman for Research and Development).

12. See, e.g., Andrew Ross Sorkin, *Pfizer Said to Be Closing In on Deal for Wyeth*, N.Y. TIMES, Jan. 24, 2009, at B1 (asserting that compared to Pfizer's impending "patent cliff," Wyeth's biologic business "is not facing the same level of patent pressures, because it is much more complicated and cost-prohibitive to make generic versions").

13. A small-molecule pharmaceutical is traditionally recognized as a "discrete chemical entity that generally would contain no more than fifty nonhydrogen atoms, most commonly carbon, nitrogen, oxygen, fluorine, chlorine, sulfur, and phosphorus." David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG L.J. 143, 154 (2005).

14. FDA, *Drugs@FDA Glossary of Terms*, <http://www.fda.gov/Cder/drugsatfda/glossary.htm#B> (last visited May 26, 2010) (defining "biological product").

15. *Id.*

16. FDA, *What Are "Biologics" Questions and Answers*, <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133077.htm> (last visited May 26, 2010).

17. See TANAZ PETIGARA & GERARD ANDERSON, *STRATEGIES TO REDUCE THE HIGH COST OF BIOLOGICS* (2008), <http://www.hpm.org/survey/us/b12/3> (explaining how biologics are usually administered in practice).

18. *Id.*; see also Amanda Brower, *Mode of Administration: A Factor in Biologic Drug Costs*, BIOTECHNOLOGY HEALTHCARE, Sept. 2004, at 64 (noting that seventy-three percent of biologic drugs in pipeline require administration by health care provider).

19. See *infra* Part II.B.2 for a discussion of the generic drug pathway.

abbreviated approval pathway for biologic copycats, known as biosimilars or follow-on biologics, is in the process of being implemented.²⁰

Biologics is a broad category that includes molecules varying widely in size and complexity.²¹ A monoclonal antibody (“mAb”) is a type of protein molecule. Therapeutic mAbs are a class of biologic drugs²² that are particularly large and highly complex.²³ Some biologics, like insulin, are relatively small and are more easily analogized to small-molecule drugs.²⁴ An antibody molecule is about twenty-five times the size of an insulin molecule.²⁵ Because greater size correlates to greater complexity,²⁶ therapeutic mAbs are particularly difficult to design and manufacture. They also often come with a staggering price tag.

Avastin, a therapeutic antibody that targets cancer cells,²⁷ costs over one hundred thousand dollars each year for a single patient.²⁸ Exorbitant costs have forced health insurers to adopt specialized policies such as requiring patients to cover a portion of the drug’s actual cost rather than paying a fixed copayment.²⁹ Those engaged in the debate have not only questioned who should pay but whether dosing should be reduced to the minimum to lower costs.³⁰ Some cancer doctors have opted to administer only half the recommended dosage of Avastin, pressured by the cost and emboldened by a study suggesting that a lower dose could be equally effective.³¹ A 2008 report by the

20. The Patient Protection and Affordable Care Act, signed into law in March 2010, included the framework for an abbreviated approval pathway for biosimilar drugs. Pub. L. No. 111-148, 124 Stat. 119 (2010) (including sections 7001–03, subtitled the “Biologics Price Competition and Innovation Act of 2009”). As of October 2010 the FDA had not yet fleshed out this framework and provided guidelines for applicants. See FDA, Implementation of the Biologics Price Competition and Innovation Act of 2009, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm> (last visited Oct. 2, 2010).

21. Rachel Behrman, FDA Director of the Office of Critical Path Programs, Opening Remarks at the FTC Roundtable on Follow-On Biologic Drugs: Framework for Competition and Continued Innovation (Nov. 21, 2008) [hereinafter FTC Roundtable] (transcript available at <http://www.ftc.gov/bc/workshops/hcbio/transcripts/081121biologicttranscript.pdf>).

22. See Stanford Medicine, Biological Therapy for Cancer Treatment, <http://cancer.stanford.edu/information/cancerTreatment/methods/biological.html> (last visited May 26, 2010) (defining different biological therapies for cancer).

23. Christian K. Schneider & Ulrich Kalinke, *Toward Biosimilar Monoclonal Antibodies*, 26 NATURE BIOTECHNOLOGY 985, 987 (2008); Michael Lanthier et al., *Economic Issues with Follow-On Protein Products*, 7 NATURE REVS. DRUG DISCOVERY 733, 733–34 (2008).

24. See Lanthier, *supra* note 23, at 737 (explaining that FDA has approved multiple insulin products under FDCA).

25. See *id.* at 734 (showing, for example, that one monoclonal antibody (Rituxan) has 1,328 amino acids while one insulin product (Novolin) has fifty-one amino acids).

26. See *id.* (charting molecular weights and amino acid lengths of biologic drugs).

27. Avastin.com, How Avastin Is Believed to Work: Starving the Tumor, <http://www.avastin.com/avastin/patient/crc/avastin/how/index.m> (last visited September 19, 2010).

28. See Pamela Jones Harbour, Comm’r, Fed. Trade Comm’n, Remarks at the ABA Antitrust and IP Conference: The Competitive Implications of Generic Biologics 2 (June 14, 2007) (transcript available at 2007 WL 2506629).

29. PETIGARA & ANDERSON, *supra* note 17, at 1–2 (describing coinsurance policies).

30. Andrew Pollack, *Cutting Dosage of Costly Drug Spurs a Debate*, N.Y. TIMES, Mar. 16, 2008, at A1.

31. *Id.* The dosage issue was also raised in the context of non-antibody therapies. Cerezyme is a treatment for Gaucher disease with a three hundred thousand dollar annual price tag. *Id.* Although only five

Congressional Budget Office estimated that passing follow-on biologics legislation would reduce expenditures on the products by twenty-five billion dollars over the next decade.³² Monoclonal antibodies represent a significant proportion of the products targeted by follow-on legislation. Manufacturers of therapeutic mAbs earned \$14.5 billion in U.S. sales during 2006,³³ representing about one-fourth of all biologic sales.³⁴

This Comment will demonstrate that therapeutic monoclonal antibodies are a distinct class of biologic drugs requiring special consideration in creating an effective follow-on biologics pathway. Part II.A provides scientific background relevant to understanding antibodies and why they present exceptional challenges. Part II.B describes the current FDA approval process for new drugs, the abbreviated approval pathway for generic small-molecule drugs, and the recently enacted framework for the abbreviated approval of biosimilars. The final portion of the Overview, Part II.C, details a federal statute permitting the licensing of government-funded inventions. Building on the policy reasons for this statute, Part III argues that the new biosimilars approval pathway should have included provisions to permit the compulsory licensing of intellectual property necessary to make a therapeutic antibody product after a reasonable exclusive marketing period expires. To support this argument, Part III.A asserts that follow-on antibody drugs will require new clinical trial data and other costly expenditures. The increased cost of entering the market will prevent a competitive market from developing unless, as Part III.B explains, legislation allows for compulsory licensing and encourages data sharing. Part III.B.2 then demonstrates how key objectives of an existing federal statute support such a provision. This Comment aims to prove that, in the case of monoclonal antibody drugs, compulsory licensing will retain incentives for innovation while creating a competitive market and increasing the safety and accessibility of modern treatments.

II. OVERVIEW

A. *Therapeutic Monoclonal Antibodies*

1. Structure and Function

To understand why antibodies pose exceptional challenges, it is informative to understand their structure. Amino acids are one of the basic building blocks of life.³⁵ End to end, amino acids link together in linear chains.³⁶ A protein is a string of amino

thousand people are taking Cerezyme worldwide, Genzyme earned 1.1 billion dollars from sales of the drug in 2007. *Id.*

32. CONG. BUDGET OFFICE, 110TH CONG., COST ESTIMATE: S. 1695 BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2007, at 1 (2008), available at <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf>.

33. Patrick G. Swann et al., *Considerations for the Development of Therapeutic Monoclonal Antibodies*, 20 CURRENT OPINION IN IMMUNOLOGY 493, 493 (2008).

34. See Lanthier, *supra* note 23, at 736 (analyzing all biologic drugs earning over \$250 million in 2006).

35. NEIL A. CAMPBELL & JANE B. REECE, BIOLOGY 64 (6th ed. 2002).

36. *Id.* at 74.

acids that twists and bends and folds into a highly specific shape.³⁷ This very specific shape, in particular the topography of the protein's surface, determines what it can bind to.³⁸

Antibodies are a type of protein molecule. Structurally, antibodies are conceptualized as having a "Y" shape.³⁹ The stalk of the "Y" designates which of five functional classes a particular antibody belongs to.⁴⁰ The stalk is relatively uniform within each class, giving each class characteristic effector functions.⁴¹ At the two tips at the top of the "Y" are the antibody's variable regions.⁴² The shape of these variable regions determines to what target that antibody will bind.⁴³ How tightly an antibody binds to a target is referred to as its affinity for the target.⁴⁴

Humans and other advanced animals produce antibodies in response to the presence of foreign material like bacteria or viruses.⁴⁵ Foreign material recognized by an antibody is an antigen.⁴⁶ When the immune system recognizes something as foreign,⁴⁷ it signals white blood cells specific for that antigen to produce armies of antibodies against it.⁴⁸ The antibodies, with their high specificity,⁴⁹ latch onto the foreign material, neutralizing it and tagging it for destruction and clearance.⁵⁰ Scientists

37. *Id.*; see also Bio-alive, Protein Structure, <http://bio-alive.com/categories/biochemistry/protein-structure.htm> (last visited May 26, 2010) (showing video depicting protein structure).

38. CAMPBELL & REECE, *supra* note 35, at 74.

39. See The University of Arizona, The Biology Project, Antibody Structure, <http://www.biology.arizona.edu/IMMUNOLOGY/tutorials/antibody/structure.html> (last visited May 26, 2010) (describing structure and exhibiting simplified graphic of an antibody).

40. See Sven Sommerfeld & Jochen Strube, *Challenges in Biotechnology Production—Generic Processes and Process Optimization for Monoclonal Antibodies*, 44 CHEMICAL ENGINEERING & PROCESSING 1123, 1124 (2005) (explaining that classes (IgM, IgG, IgA, IgD, and IgE) are characterized by similar amino acid sequences in Fc region and accordingly have similar biological functions); see also W.H. Freeman, Human Immunoglobulins, <http://www.whfreeman.com/kuby/content/anm/kb06an01.htm> (last visited May 26, 2010) (showing visual representation of "Y"-shaped antibodies).

41. DAVID MALE ET AL., IMMUNOLOGY 61–62 (7th ed. 2006). For example, one class of antibodies directs the immune system to destroy the cell it is attached to. *Id.* at 72.

42. The University of Arizona, *supra* note 39.

43. See *id.* (stating isolated regions referred to as hypervariable regions or complementarity determining regions typically determine affinity of an antibody for a given antigen).

44. MALE ET AL., *supra* note 41, at 68.

45. See Bio-alive, Specific Immunity, Antibodies, <http://bio-alive.com/categories/immunology/antibodies.htm> (last visited May 26, 2010) (explaining immune response through animation).

46. See *id.* (explaining relationship between antibodies and antigens through animation).

47. This can be a substance from outside the body, or a self-antigen that the immune system erroneously believes is non-self (triggering an auto-immune reaction). P.K. GUPTA, CELL & MOLECULAR BIOLOGY 864–65 (2008).

48. The white blood cells, specifically B cells, divide and differentiate into an antibody-secreting cell type. Ian C. MacLennan & Deborah L. Hardie, *The Dynamic Structure of Antibody Responses*, in MOLECULAR BIOLOGY OF B CELLS 187, 187 (Tasuku Honjo et al. eds., 2004).

49. See Eric J. Sundberg & Roy A. Mariuzza, *Antibody Structure and Recognition of Antigen*, in MOLECULAR BIOLOGY OF B CELLS, *supra* note 48, at 491, 492 (explaining that antibodies and their targets "exhibit a high degree of both shape and chemical complementarity at their interacting surfaces").

50. See MALE ET AL., *supra* note 41, at 11, 13 (indicating ways in which immune system can eradicate foreign materials).

estimate that the human body is capable of producing antibodies specific to between ten million and one billion targets.⁵¹

Scientists have harnessed the extraordinary natural specificity of antibodies and altered the molecules to create versatile therapeutic tools.⁵² They are employed to mask surface proteins, tag unwanted cells for destruction, and act as carriers, delivering harmful or helpful molecules with high specificity.⁵³ A scientist can develop an antibody to bind to specific foreign invaders or to human cells that are cancerous.⁵⁴ The designation “monoclonal” simply means that all the antibodies composing the therapy bind to the exact same, highly specific target.⁵⁵ Antibodies have the potential to treat conditions varying from cancer⁵⁶ to psoriasis⁵⁷ to viral infections.⁵⁸

2. Developing Antibodies for Therapeutic Use

Monoclonal antibody therapies are possible because of a breakthrough by two scientists in 1975.⁵⁹ Kohler and Milstein developed hybridomas,⁶⁰ fusions of cancerous B cells and B cells derived from mice immunized with the target antigen.⁶¹ The resulting hybridomas were essentially self-replicating antibody factories.⁶² However,

51. Linda M. Hendershot & Roberto Sitia, *Immunoglobulin Assembly and Secretion*, in *MOLECULAR BIOLOGY OF B CELLS*, *supra* note 48, at 261, 261.

52. *See* Louis M. Weiner, *Fully Human Therapeutic Monoclonal Antibodies*, 29 *J. IMMUNOTHERAPY* 1, 1 (2006) (listing range of therapeutic targets and mechanisms of action).

53. *Id.*

54. *See* Swann et al., *supra* note 33, at 493 (explaining diversity of mAb-related products in development).

55. *See* Pacific Immunology, *Types of Antibodies*, <http://www.pacificimmunology.com/types-of-antibodies.asp> (last visited May 26, 2010) (distinguishing polyclonal and monoclonal antibodies and explaining that former has broad research applications but latter is advantageous for therapeutic applications).

56. *See generally* Robert K. Oldham & Robert O. Dillman, *Monoclonal Antibodies in Cancer Therapy: 25 Years of Progress*, 26 *J. CLINICAL ONCOLOGY* 1774 (2008).

57. *See generally* Yulia Vugmeyster et al., *Efalizumab (anti-CD11a)-Induced Increase in Peripheral Blood Leukocytes in Psoriasis Patients Is Preferentially Mediated by Altered Trafficking of Memory CD8+ T Cells into Lesional Skin*, 113 *CLINICAL IMMUNOLOGY* 38 (2004).

58. *See* Z.Y. Keck et al., *Therapeutic Control of Hepatitis C Virus: The Role of Neutralizing Monoclonal Antibodies*, in *HUMAN ANTIBODY THERAPEUTICS FOR VIRAL DISEASE 1*, 1–3 (Scott K. Dessain ed., 2008) (proposing HCV treatment utilizing both antiviral drugs and virus neutralizing antibodies).

59. A. Nissim & Y. Chernajovsky, *Historical Development of Monoclonal Antibody Therapeutics*, 181 *HANDBOOK OF EXPERIMENTAL PHARMACOLOGY* 3, 4 (2008).

60. *Id.*

61. *Id.*; *see also* Weiner, *supra* note 52, at 2 (explaining how Kohler and Milstein developed hybridomas by fusing plasma cells and myeloma cells). Plasma cells are healthy B cells that have differentiated into antibody production factories after recognizing an antigen. MALE ET AL., *supra* note 41, at 13. Myeloma cells are cancerous plasma cells. Multiple Myeloma Research Foundation, *Newly Diagnosed Patients: What Is Multiple Myeloma*, <http://www.themmr.org/living-with-multiple-myeloma/newly-diagnosed-patients/what-is-multiple-myeloma/about-multiple-myeloma.html> (last visited May 26, 2010).

62. The normal plasma cells derived from the mouse contained instructions to act as antibody factories. Cancerous cells are cells gone awry that grow at an increased rate and reproduce perpetually. National Cancer Institute, *What Is Cancer?*, <http://www.cancer.gov/cancertopics/what-is-cancer> (last visited May 26, 2010). Thus, fusing the two types of cells created fast-growing, inexhaustible antibody factories.

since murine cells⁶³ produced the antibodies, the antibodies displayed molecular patterns that the human immune system recognized as foreign. This severely limited the *in vivo* therapeutic potential of the first mAbs.⁶⁴ OKT3, a murine mAb, was approved by the FDA in 1986 to treat organ transplant rejection.⁶⁵ No other fully mouse antibody was ever approved.⁶⁶

Scientists developed ways to mask the murine features and to combine the essential murine regions with parts of human antibodies creating chimeric antibodies.⁶⁷ It was only thirteen years ago that the FDA approved the first mAb to treat cancer.⁶⁸ Researchers are also now developing completely humanized antibodies and transgenic mice⁶⁹ that produce human antibodies.⁷⁰ While both of these techniques still involve the creation of hybridomas, even that is being phased out.⁷¹

3. Commercial Manufacture: Current Practices and Safety Concerns

A small-molecule pharmaceutical is produced through a stepwise chemical synthesis that is highly reproducible. The resulting product is then characterized with standardized techniques.⁷² Biologic drug production is starkly different. One cannot mix together certain chemicals in a certain order and produce a monoclonal antibody. Rather, scientists must transform living cells, like the hybridomas described above, into antibody production factories.⁷³ Manufacturers must then grow large-scale cell suspensions and isolate the antibody proteins through complex purification procedures.⁷⁴ As the cells ferment in the growth medium, they excrete the antibodies.⁷⁵

63. Murine is an adjective denoting derivation from a rodent. See Biology Online, Murine, <http://www.biology-online.org/dictionary/Murine> (last visited May 26, 2010) (defining “murine” as “[o]f, relating to, a member of the rodent family muridae, including rats and mice”). Thus murine cells are simply mouse cells.

64. Peter J. Hudson & Christelle Souriau, *Engineered Antibodies*, 9 NATURE MED. 129, 129 (2003).

65. Trisha Gura, *Magic Bullets Hit the Target*, 417 NATURE 584, 585 (2002).

66. *Id.*

67. Swann et al., *supra* note 33, at 493.

68. Bruce D. Cheson & John P. Leonard, *Monoclonal Antibody Therapy for B-Cell Non-Hodgkin's Lymphoma*, 359 NEW ENG. J. MED. 613, 613 (2008). The drug was Rituximab, a chimeric antibody that added murine variable regions to a human antibody. *Id.* at 616. Today Rituximab is a part of the initial standard treatment cocktail for large B-cell lymphoma patients. *Id.* at 618.

69. Transgenic animals are animals expressing the DNA of another species. Biotechnology Industry Organization, Transgenic Animals: Frequently Asked Questions, <http://www.bio.org/animals/faq.asp> (last visited May 26, 2010). A mouse expressing human DNA is a transgenic mouse.

70. Hudson & Souriau, *supra* note 64, at 129.

71. Scientists are now employing synthetic antibody libraries to select the molecules specific for a given target. James D. Marks, *Monoclonal Antibodies from Display Libraries*, in MOLECULAR BIOLOGY OF B CELLS, *supra* note 48, at 511, 513.

72. See Dudzinski, *supra* note 13, at 155 (explaining that success of small-molecule paradigm reflects relative simplicity of molecules and reliability of their production).

73. Feng Li et al., *Current Therapeutic Antibody Production and Process Optimization*, BIOPROCESSING J., Sept.–Oct. 2005, at 1, 1–2. Circular pieces of DNA encoding instructions for the antibody of interest are put into cells. The cells, using their innate machinery, read the instructions and secrete the antibodies. See *id.* (describing monoclonal antibody production).

74. See Lily Chu & David K. Robinson, *Industrial Choices for Protein Production by Large-Scale Cell Culture*, 12 CURRENT OPINION IN BIOTECHNOLOGY 180, 182 (2001) (listing production techniques of specific

The antibodies must then be (1) captured, (2) purified, and (3) optimized.⁷⁶ These steps are designed to produce the desired concentration of the product and ensure safety by removing any contaminants.⁷⁷ Unlike chemicals mixed to produce small-molecule drugs, the cells producing biologics are living, growing, changing organisms endowed with the vulnerability and lack of predictability inherent in all living things.

For some, biologics characterization procedures that reveal structure and predict function can mitigate the dangers of the inevitable manufacturing inconsistencies.⁷⁸ However, mAbs are so complex that current characterization techniques are insufficient, leaving serious questions about the safety and efficacy of potential follow-on products.⁷⁹

i. Immunogenicity and Biologics in General

A significant safety and efficacy issue with all biologic drugs is immunogenicity.⁸⁰ Immunogenicity is defined as the tendency to cause a reaction in a patient's immune system.⁸¹ A reaction may result when the immune system identifies a biologic drug as a foreign invader.⁸²

A litany of variables can cause a biologic product to deviate from its intended shape or interact unexpectedly in a patient's body. Immunogenic properties can result from the design of the molecule, from unintended changes to it during manufacture,⁸³ and from heterogeneous clinical factors.⁸⁴ Even minor changes to the shape of the drug molecule can change how a patient's immune system responds to the drug, leading to unanticipated immunogenicity.⁸⁵

monoclonal antibody products in table 1). Manufacturers typically use one of four mammalian cell lines to produce monoclonal antibodies. Sommerfeld & Strube, *supra* note 40, at 1126. A cell line is a population of cell clones that reproduce in perpetuity. In contrast to the industry standard, Merck is embarking on a novel strategy of using yeast cells to produce biologic drugs. Jonathan D. Rockoff & Ron Winslow, *Merck to Develop Biotech Generics—Its First Copycat Drug Would Compete with Amgen's Aranesp and Is Scheduled for Launch in 2012*, WALL ST. J., Dec. 10, 2008, at B1.

75. Sommerfeld & Strube, *supra* note 40, at 1126.

76. *Id.* at 1127.

77. *Id.*

78. Schneider & Kalinke, *supra* note 23, at 987.

79. *Id.* at 987–88.

80. See generally Adam Cheifetz & Lloyd Mayer, *Monoclonal Antibodies, Immunogenicity, and Associated Infusion Reactions*, 72 MOUNT SINAI J. MED. 250 (2005).

81. R.T. Purcell & R.F. Lockey, *Immunologic Responses to Therapeutic Biologic Agents*, 18 J. INVESTIGATIONAL ALLERGOLOGY & CLINICAL IMMUNOLOGY 335, 336 (2008).

82. Cheifetz & Mayer, *supra* note 80, at 251. In addition to the activation of a classic immune cascade by a foreign epitope, biologic drugs can induce poorly understood anti-self reactions. Anne S. De Groot & David W. Scott, *Immunogenicity of Protein Therapeutics*, 28 TRENDS IN IMMUNOLOGY 482, 482 (2007).

83. TIMOTHY D. COAN & RON ELLIS, *GENERIC BIOLOGICS: THE NEXT FRONTIER* 10 (2001), <http://www.theraproteins.com/Generics%20Biologics%20the%20next%20frontier.pdf>.

84. Swann et al., *supra* note 33, at 495 (listing “clinical factors such as the patient population, heterogeneity of the disease, intercurrent illnesses that disrupt the distribution of proteins, concomitant medications, dose, route of administration, and pre-existing antibodies”).

85. COAN & ELLIS, *supra* note 83, at 10.

Immunogenicity reactions range in severity.⁸⁶ A mild reaction will only result in reduced efficacy due to neutralization or destruction of a portion of the drug by the patient's immune system.⁸⁷ Stronger reactions can cause mild to severe side effects, posing a significant safety risk.⁸⁸ One such severe occurrence is cytokine release syndrome wherein a patient's immune system triggers the release of molecular messengers in reaction to the foreign material.⁸⁹ Major cytokine-release syndrome is a condition unique to biologic therapies in which the body releases a potentially fatal quantity of cytokines.⁹⁰

ii. *Sources of Immunogenicity*

Scientists can insert perfect instructions into a cell to direct the production of antibodies and precisely control growth conditions but, until clinical studies are done, cannot predict the safety profile of the product.⁹¹ For instance, the characteristics of the carbohydrates appended to the molecule can result in unanticipated immunogenicity.⁹² Adding carbohydrates, a process called glycosylation, is key to the proper folding of the molecule, its stability and interactions with other molecules, and, subsequently, its immunogenicity.⁹³ Most therapeutic monoclonal antibodies are glycosylated in only one, or maybe two, consistent locations.⁹⁴ However, the composition and structure of the chain is not always consistent because it changes depending on the cell line and cell culture environment.⁹⁵

86. See Robin Thorpe & Meenu Wadhwa, *Protein Therapeutics and Their Immunogenicity*, in BIOPHARMACEUTICALS FOR EUROPEAN HOSPITAL PHARMACISTS 27, 27–28 (Huub Schellekens & Arnold G. Vulto eds., 2008) (discussing range of reactions).

87. Gopi Shankar et al., *A Risk-Based Bioanalytical Strategy for the Assessment of Antibody Immune Responses Against Biological Drugs*, 25 NATURE BIOTECHNOLOGY 555, 555–56 (2007).

88. Physicians administering FDA-approved therapeutic antibodies have observed “infusion reactions” in approximately five to ten percent of infusions. Cheifetz & Mayer, *supra* note 80, at 250.

89. See Scott Plevy et al., *A Phase I Study of Visilizumab, a Humanized Anti-CD3 Monoclonal Antibody, in Severe Steroid-Refractory Ulcerative Colitis*, 133 GASTROENTEROLOGY 1414, 1421 (2007) (reporting eighty-eight percent of patients experienced cytokine release symptoms after treatment with monoclonal antibody drug).

90. John C. Morris & James F. Holland, *Oncologic Emergencies*, in HOLLAND-FREI CANCER MEDICINE 367–68, (Robert C. Bast, Jr. et al., eds., 5th ed. 2000), available at <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=cmed.section.41572>.

91. See Thorpe & Wadhwa, *supra* note 86, at 28–29 (explaining unpredictable nature of immunogenicity reactions).

92. See Harald H. Sitte, *Biologicals, Biosimilars, Drug Substitution: A Mandatory Sequence?*, in BIOPHARMACEUTICALS FOR EUROPEAN HOSPITAL PHARMACISTS, *supra* note 86, at 36, 36–38 (differentiating protein production in mammalian cells and *E. coli* cells).

93. Hendershot & Sitia, *supra* note 51, at 262.

94. Amareth Lim et al., *Glycosylation Profiling of a Therapeutic Recombinant Monoclonal Antibody with Two N-Linked Glycosylation Sites Using Liquid Chromatography Coupled to a Hybrid Quadrupole Time-of-Flight Mass Spectrometer*, 375 ANALYTICAL BIOCHEMISTRY 163, 164 (2008).

95. See *id.* (showing that glycosylation profiles of monoclonal antibody should be gauged to ensure consistency); Sommerfeld & Strube, *supra* note 40, at 1126 (explaining that glycosylation pattern is important factor when selecting appropriate cell line).

Another serious immunogenicity issue is the aggregation of the product.⁹⁶ Antibodies, like all proteins, can bunch together.⁹⁷ Small clumps can lead to increased immunogenicity reactions in patients, and larger clumps can interfere with the administration of the drug.⁹⁸ Experts report that aggregation problems in therapeutic protein manufacture are “not uncommon.”⁹⁹ Even slight changes in the manufacturing process, like changing the growth medium, can significantly alter aggregation.¹⁰⁰ Aggregation can occur at any step in the production process: during production, purification, or storage.¹⁰¹

Cell-culture contamination is a persisting issue for therapeutic biologics manufacturers, especially in large-scale production.¹⁰² Living cells need food and are typically grown in serum.¹⁰³ As serum is an animal product, it can contaminate the drug mixture with animal proteins and other undesirables.¹⁰⁴ Contaminants such as DNA, toxins, and viruses are of serious concern. Manufacturers deal with this threat with additives to the growth medium and through purification. However, the more purification steps, the more antibody product is lost.¹⁰⁵ Other chemically reactive contaminants, even exposure to light, can cause protein structure changes and lead to increased immunogenicity.¹⁰⁶

With all of these uncertain factors interacting, serious safety concerns persist.¹⁰⁷ A recent editorial examining immunogenicity studies opined that “predicting and identifying the cause of immunogenicity is almost impossible.”¹⁰⁸ Relevant to the production of follow-on biologics, Purcell and Lockey conclude that “[e]xperience has demonstrated that [biologics], although highly effective, are capable of a wide range of unusual and atypical reactions, some of which can be life-threatening. As older biologic

96. See John F. Carpenter et al., *Overlooking Subvisible Particles in Therapeutic Protein Products: Gaps That May Compromise Product Quality*, 98 J. PHARMACEUTICAL SCIENCES 1201, 1202–03 (2009) (discussing impact of aggregation on immunogenicity).

97. Mary E.M. Cromwell et al., *Protein Aggregation and Bioprocessing*, 8 AAPS J. E572, E572 (2006), available at <http://www.aapsj.org/articles/aapsj0803/aapsj080366/aapsj080366.pdf>.

98. *Id.*

99. *Id.*

100. *Id.* at E574.

101. Carpenter et al., *supra* note 96, at 1202.

102. Chu & Robinson, *supra* note 74, at 185. Contamination can arise from viruses present in the animal serum or from bacteria accidentally introduced during processing. *Id.*

103. See Sommerfeld & Strube, *supra* note 40, at 1126 (noting that adapting cells to serum-free medium is time-consuming process but saves money overall since purification yields can double). However, components of these serum-free mediums may still be animal derived, meaning similar risks persist. Keith L. Carson, *Flexibility—The Guiding Principle for Antibody Manufacturing*, 23 NATURE BIOTECHNOLOGY 1054, 1057 (2005).

104. Sommerfeld & Strube, *supra* note 40, at 1126.

105. Carson, *supra* note 103, at 1057.

106. See Basant Sharma, *Immunogenicity of Therapeutic Proteins. Part 1: Impact of Product Handling*, 25 BIOTECHNOLOGY ADVANCES 310, 312 (2007) (explaining oxidation).

107. See generally *id.*

108. Jean-Hugues Trouvin, Editorial, *Introductory Note to the Three-Part Series of Papers by B Sharma on: Immunogenicity of Therapeutic Proteins: How to Assess and the Role of Pharmaceutical Quality*, 25 BIOTECHNOLOGY ADVANCES 307, 307 (2007).

agents go off patent, subtle production alterations have the potential to cause immune reactions”¹⁰⁹

B. FDA Drug Approvals

1. NDAs, BLAs, and TMOAs (Twelve Million Other Acronyms)

A manufacturer may not market a new drug until it receives FDA approval.¹¹⁰ The terms “drug”¹¹¹ and “new drug” are both terms of art. “New drug” encompasses all drugs that are “not generally recognized, among experts . . . as safe and effective.”¹¹² In practice, all drug products new to the market, including generics and altered existing products, are required to undergo FDA approval.¹¹³

Generally, small-molecule pharmaceuticals and therapeutic biologics are both classified as drugs,¹¹⁴ but undergo separate, “nearly identical” approval processes.¹¹⁵ Small-molecule drugs obtain approval through a new drug application (“NDA”) pursuant to the Food, Drug, and Cosmetic Act (“FDCA”).¹¹⁶ Instead of filing for an NDA, the manufacturer of a biologic must file a biologics license application (“BLA”).¹¹⁷ BLAs are filed pursuant to the Public Health Service Act (“PHSA”) and directed to a subset of the FDA, the Center for Biologics Evaluation and Research (“CBER”) which handles the premarket approval proceedings.¹¹⁸ The FDA retains the responsibility of establishing regulations to control the approval of biologic products.¹¹⁹ Section 262 of the PHSA sets the foundation for these regulations, stating

109. Purcell & Lockey, *supra* note 81, at 340.

110. 21 U.S.C. § 355(a) (2006).

111. *Id.* § 321(g)(1) (providing multipart definition of drug including “articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals”). See generally Jay M. Zitter, *What Is “Drug” Within Meaning of § 201(g)(1) of Federal Food, Drug, and Cosmetic Act (21 USCS § 321(g)(1))*, 127 A.L.R. FED. 141 (1995).

112. 21 U.S.C. § 321(p)(1). Although the language suggests the opinion of experts alone demonstrates that a product is generally recognized as safe and effective (“GRASE”), the testimony of physicians or scientists is not enough. See LARS NOAH, LAW, MEDICINE, AND MEDICAL TECHNOLOGY: CASES AND MATERIALS 49 n.4 (2d ed. 2007) (explaining that expert agreement cannot be recent development, but must be corroborated by medical literature and supported on foundation of sufficient age).

113. For a comprehensive review of the approval process, see Kathryn C. Zoon & Robert A. Yetter, *The Regulation of Drugs and Biological Products by the Food and Drug Administration*, in PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH 97, 100–07 (John I. Gallin & Frederick P. Ognibene eds., 2d ed. 2007).

114. See *United States v. Lorán Med. Sys., Inc.*, 25 F. Supp. 2d 1082, 1084–86 (C.D. Cal. 1997) (finding neonatal rabbit and human fetal cells injected into patients qualify as biologics and fall within § 321(g)(1) definition of a drug).

115. Lars Noah, *Managing Biotechnology’s [R]evolution: Has Guarded Enthusiasm Become Benign Neglect?*, VA. J.L. & TECH., Spring 2006, at 1, 20, http://www.vjolt.net/vol11/issue2/v11i2_a4-Noah.pdf.

116. 21 U.S.C. § 355.

117. 42 U.S.C. § 262(a) (2006).

118. FDA, About CBER, <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm123340.htm> (last visited Oct. 17, 2010).

119. 42 U.S.C. § 262(a)(2).

that an approved product must be “safe, pure, and potent.”¹²⁰ The regulations promulgated by the FDA require applicants to “submit data derived from nonclinical laboratory and clinical studies” as well as an explanation of the manufacturing procedures.¹²¹

FDA regulations set the clinical trial requirements for obtaining an NDA or BLA.¹²² For most drug approvals, three phases of clinical trials are necessary.¹²³ Phase I investigates basic safety of the treatment and usually only involves twenty to eighty human subjects.¹²⁴ A treatment that passes phase I is then evaluated for efficacy in larger trials involving up to a few hundred patients with the targeted condition or disease.¹²⁵ The final phase, phase III, can include several hundred to several thousand individuals and is “intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling.”¹²⁶ Phase III trials are the most expensive, the average study costing eighty-six million dollars,¹²⁷ and typically take four years to complete.¹²⁸

2. Hatch-Waxman: Generic Pathway for Drugs Approved Under the FDCA

Until the enactment of the Hatch-Waxman Act in 1984,¹²⁹ the only way to obtain approval to market a new small-molecule drug was to undergo the complete NDA process.¹³⁰ The FDA’s NDA requirements are stringent and require a large investment of time and money by the manufacturer.¹³¹ The requirements were (and remain) necessary to ensure safety and efficacy but created a system in which the introduction of generic products was not economically feasible.¹³² Though a drug’s patent term

120. *Id.* § 262(a)(2)(C) (requiring also that manufacturing facility will “assure that the biological product continues to be safe, pure, and potent”).

121. 21 C.F.R. § 601.2(a) (2010).

122. *Id.* § 312.2(a) (stating that § 312 “applies to all clinical investigations of products that are subject to section 505 of the [FDCA] or to the licensing provisions of the [PHSA]”).

123. *Id.* § 312.21.

124. *Id.* § 312.21(a).

125. *Id.* § 312.21(b).

126. *Id.* § 312.21(c).

127. Henry G. Grabowski et al., *Entry and Competition in Generic Biologics*, 28 *MANAGERIAL & DECISION ECON.* 439, 442 (2007).

128. Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-On Biologics in the United States*, 35 *FLA. ST. U. L. REV.* 555, 566 (2008).

129. Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (codified as amended in scattered sections of 15, 21, 25, and 42 U.S.C.).

130. See generally Thomas Chen, Note, *Authorized Generics: A Prescription for Hatch-Waxman Reform*, 93 *VA. L. REV.* 459, 462–63 (2007).

131. See NOAH, *supra* note 112, at 231 n.3 (noting that bringing drug to market takes on average twelve years and over one billion dollars).

132. See Dudzinski, *supra* note 13, at 169 (noting that, because of high investment costs for NDA, there were 150 pioneer drugs without any generic copies available).

expired, other manufacturers could not afford to invest in obtaining FDA approval and subsequently sell the product as a lower-priced generic.¹³³

Congress acknowledged the need for an expedited approval process to end this “de facto extension of drug patents.”¹³⁴ The final legislation, formally titled the Drug Price Competition and Patent Term Restoration Act, was a compromise aimed at bringing cheaper drugs to market while retaining strong incentives for innovation.¹³⁵

Hatch-Waxman created an alternative to the NDA, an abbreviated new drug application (“ANDA”).¹³⁶ A manufacturer who files an ANDA does not need to repeat clinical trials performed by the pioneer drug maker to prove safety and efficacy.¹³⁷ The ANDA filer need only demonstrate that the listed drug and the generic compound are pharmaceutically equivalent¹³⁸ and bioequivalent.¹³⁹ This involves standard lab tests showing that the compounds are identical and *in vivo* tests showing that the generic compound is absorbed at a similar rate. Once data proving bioequivalence is shown, the generic maker can rely on published literature and the pioneer’s data to satisfy the safety and efficacy requirements.¹⁴⁰ Hatch-Waxman thus eliminates the inefficiency of repeating the same studies every time a new manufacturer enters the market.¹⁴¹ The ability to skip clinical trial testing also eliminates more than ninety-nine percent of the FDA approval costs, saving each generic manufacturer hundreds of millions of dollars.¹⁴² This has allowed the generic drug business to flourish, increasing market competition and lowering prices for consumers.¹⁴³

133. See *id.* (recounting events leading up to Hatch-Waxman).

134. Chen, *supra* note 130, at 463; see also H.R. REP. NO. 98-857 pt. 2, at 4 (1984), reprinted in 1984 U.S.C.C.A.N. 2686, 2688 (noting practical extension of patent monopoly due to FDA rules regarding generics).

135. See H.R. REP. NO. 98-857 pt. 2, at 5–7, reprinted in 1984 U.S.C.C.A.N. at 2689–91 (summarizing two components of bill and noting proponents described it as “compromise between two competing economic interests”).

136. 21 U.S.C. § 355(j) (2006). Applicants can also seek expedited approval through § 355(b)(2), which creates a pathway for drugs nearly identical to those already approved, such as generics with a different dosage. Gitter, *supra* note 128, at 569–71.

137. See Gitter, *supra* note 128, at 568–69 (explaining that some clinical and scientific data is still required, but significant expense of repeating clinical trials to prove safety and efficacy is not).

138. Pharmaceutical equivalents are drugs having the same active ingredient(s), dosage form, route of administration, and strength or concentration. FDA, Drugs@FDA Glossary of Terms, <http://www.fda.gov/Cder/drugsatfda/glossary.htm#P> (last visited Oct. 17, 2010) (defining “pharmaceutical equivalents”).

139. 21 U.S.C. § 355(j)(2)(A)(iv). “A drug shall be considered to be bioequivalent to a listed drug if . . . the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug” *Id.* § 355(j)(8)(B)(i).

140. While the FDA relies on the pioneer’s data in approving the generic drug, it will not provide the generic manufacturer with the actual data. Gitter, *supra* note 128, at 571.

141. William E. Ridgway, Note, *Realizing Two-Tiered Innovation Policy Through Drug Regulation*, 58 STAN. L. REV. 1221, 1227 (2006).

142. See Gitter, *supra* note 128, at 571 (reporting that complete NDA costs around \$800 million while obtaining approval for generic drugs costs only around one or two million).

143. See Saami Zain, *Sword or Shield? An Overview and Competitive Analysis of the Marketing of “Authorized Generics,”* 62 FOOD & DRUG L.J. 739, 742 (2007) (discussing brand-name manufacturer tactics to recoup loss of market share).

In addition to altering the drug approval process, Hatch-Waxman includes provisions dealing with intellectual property issues, aiming to provide sufficient monetary incentives for innovation.¹⁴⁴ One provision, found in the FDCA, provides innovators with market exclusivity, and another provision, in the Patent Act, provides the potential for patent term restoration.¹⁴⁵ The patent term restoration provision allows pioneer drug makers to apply for a patent extension equivalent to the amount of marketing time lost from the date of NDA filing to FDA approval.¹⁴⁶ In practice this means that if the active ingredient of the drug is covered by a strong patent, the pioneer can enjoy an exclusive market for up to fourteen years.¹⁴⁷

Hatch-Waxman also created the FDCA market exclusivity provision which guarantees a manufacturer five years of market exclusivity upon approval of an NDA for a new molecular entity.¹⁴⁸ This exclusivity is a separate form of intellectual property rights than patent rights.¹⁴⁹ A generic manufacturer must wait four years to even file an ANDA.¹⁵⁰ Prior to Hatch-Waxman, competitors could not develop a competing drug until after patent expiration because experimentation would infringe on the patent. Hatch-Waxman permits potential ANDA applicants to experiment without infringing.¹⁵¹ The generic product can then be ready to enter the market contemporaneously with the end of the five-year exclusivity period or upon patent expiration.¹⁵²

Hatch-Waxman entices generic applicants to challenge pioneer drug patents. When applying for an ANDA, a generic manufacturer can file a paragraph IV certification stating that “such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.”¹⁵³ A paragraph IV certification is a statutory act of infringement¹⁵⁴ providing the pioneer the

144. H.R. REP. NO. 98-857 pt. 2, at 6 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2690.

145. 21 U.S.C. § 355(c)(3)(E)(ii) (2006); 35 U.S.C. § 156 (2006).

146. 35 U.S.C. § 156(c). The amount of restored time can be up to five years, and the total years of marketing time with the restoration period added on cannot exceed fourteen years. *Id.* § 156(c)(3); Tamsen Valoir, *Six Methods of Preserving Market Exclusivity*, 18 INTELL. PROP. & TECH. L.J., Nov. 2006, at 12, 12 (2006).

147. Valoir, *supra* note 146, at 12–13.

148. 21 U.S.C. § 355(c)(3)(E)(ii).

149. ALEX M. BRILL, PROPER DURATION OF DATA EXCLUSIVITY FOR GENERIC BIOLOGICS: A CRITIQUE 2 (2008), *available at* http://www.tevad.com/Brill_Exclusivity_in_Biogenics.pdf (white paper funded by Teva Pharmaceuticals). The government grant of data exclusivity is not challengeable in court, in contrast to patents which are commonly destroyed in litigation. *Id.* at 6.

150. 21 U.S.C. § 355(c)(3)(E)(ii) (providing that “an application may be submitted . . . after the expiration of four years from the date of the approval of the subsection (b) application if it contains” a paragraph IV certification).

151. 35 U.S.C. § 271(e)(1).

152. Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 190 (1999).

153. 21 U.S.C. § 355(j)(2)(A)(vii)(IV); *see also* SUSAN DESANTI ET AL., FED. TRADE COMM’N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 8 (2002), *available at* <http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf> (providing graphical presentation of Paragraph IV certification process).

154. 35 U.S.C. § 271(e)(2).

opportunity to initiate an infringement action.¹⁵⁵ From 1998 to 2000, twenty percent of ANDA applicants filed paragraph IV certifications, seeking market entry before the patent's expiration date.¹⁵⁶ To incentivize patent challenges, a successful paragraph IV challenge earns an ANDA filer 180 days of generic market exclusivity.¹⁵⁷ Generic makers can scoop up eighty percent of the market within two months just by pricing their product fifteen to twenty percent lower than the brand product.¹⁵⁸

Brand drug makers have also devised ways of extending their exclusivity unintended by the framers of Hatch-Waxman. To defend their market share, brand makers employ tactics such as marketing authorized generics,¹⁵⁹ offering generic drug makers payments to delay market entry,¹⁶⁰ and removing patent listings before paragraph IV certifications are filed.¹⁶¹

The FDA has made clear that Hatch-Waxman only creates an abbreviated application pathway for generic versions of NDA approved drugs and not for copycats of BLA-approved drugs.¹⁶² Over the past two decades, the FDA has approved a few copycat biologic treatments,¹⁶³ but only for products originally approved through an NDA.¹⁶⁴ In one such approval letter, the FDA was very careful to distinguish the

155. 21 U.S.C. § 355(j)(5)(B)(iii).

156. SUSAN DESANTI ET AL., *supra* note 153, at ii.

157. 21 U.S.C. § 355(j)(5)(B)(iv).

158. Gregory Glass, *Authorized Generics*, 4 NATURE REVS. DRUG DISCOVERY 953, 953 (2005).

159. See generally Generic Pharmaceutical Association, *Authorized Generics*, <http://www.gpha.org/issues/authorized-generics> (last visited Oct. 17, 2010). To capture some of the generic market, the pioneer manufacturer introduces a second line of their own product when their patent expires. *Id.* This product is identical to the branded version, which continues to be marketed at a high price but has a generic label and a generic price. *Id.*

160. See, e.g., *In re Cardizem CD Antitrust Litig.*, 105 F. Supp. 2d 618, 623 (E.D. Mich. 2000) (refusing to dismiss plaintiff's challenge to agreement by brand drug maker to pay generic maker forty million dollars a year not to sell its product). Congress sought to stop these agreements with a 2003 amendment to the Hatch-Waxman Act. NOAH, *supra* note 112, at 911 n.3. Many courts have found that these actions amount to antitrust violations by drug companies. See David E. Swarts, Note, *Still on the Hook: Why the Hatch-Waxman Act Does Not Provide Drug Companies Immunization from the Antitrust Laws*, 54 RUTGERS L. REV. 563, 570–76 (2002) (discussing cases prior to 2003 amendment where courts found agreements between generic and name-brand drug companies to be antitrust violations). However, others emphasize such agreements are not per se illegal. See, e.g., *Schering-Plough Corp. v. Fed. Trade Comm'n*, 402 F.3d 1056, 1076 (11th Cir. 2005) (resolving that private settlements blocking generic entry are not conclusively antitrust problems).

161. See *Teva Pharm., USA, Inc. v. Leavitt*, 548 F.3d 103, 108 (D.C. Cir. 2008) (finding that removing patent listing in anticipation of Paragraph IV certification is not unlawful).

162. Lester M. Crawford, *The Law of Biologic Medicine*, statement before the Senate Committee on the Judiciary, June 23, 2004, available at <http://www.fda.gov/NewsEvents/Testimony/ucm113745.htm>.

163. See, e.g., *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313, 1320–22 (D.C. Cir. 1998) (giving deference to FDA's determination of "sameness" and affirming approval of Ferring's ANDA despite differences in active and inactive ingredients).

164. See Henry Grabowski et al., *The Market for Follow-On Biologics: How Will It Evolve?*, 25 HEALTH AFF. 1291, 1292 (2006) (explaining that some early biologics like human growth hormone were approved as new drugs pursuant to FDCA). If the pioneer drug was approved through an NDA, an abbreviated application is possible. In 2003 Sandoz submitted a 505(b)(2) application for a recombinant growth hormone, Omnitrope. *Sandoz, Inc. v. Leavitt*, 427 F. Supp. 2d 29, 32 (D.D.C. 2006). The FDA approved the application but emphasized the exceptional nature of the situation, stressing that the innovator product was approved under the FDCA, not the PHSA. Letter from Steven K. Galson, Dir., Ctr. for Drug Evaluation & Research, Dep't of

approved follow-on product from more complex biologics.¹⁶⁵ Only one or two additional follow-on biologics are expected to obtain FDA approval by 2010.¹⁶⁶ Almost all biologics are now approved through BLAs pursuant to the Public Health Service Act.¹⁶⁷ For these treatments, no abbreviated pathway is yet in use. Without an effective biosimilar pathway, a competitive biologic industry cannot develop.¹⁶⁸

3. Economic Models, Proposed Legislation, and the Enacted Law

The key features of the proposed biosimilars bills were the amount of market exclusivity they granted to the pioneer manufacturer, whether the first-to-file FOB manufacturer received market exclusivity, the definitions of key terms of art, and their patent challenge schemes.¹⁶⁹ Economists have designed models addressing the pioneer exclusivity issue.¹⁷⁰ A predominant voice on the subject, Henry Grabowski, asserted that around fourteen years is the optimal exclusivity award.¹⁷¹ However, this figure was recently critiqued by another scholar, Alex Brill, who fixed the appropriate period at seven years.¹⁷² At least one organization has argued that patent rights are sufficient incentives and no exclusivity period should exist.¹⁷³

Mirroring the uncertainty in academia, bills introduced in Congress ranged in their exclusivity grants from no exclusivity to fifteen years of exclusivity.¹⁷⁴ Congressmen

Health & Human Servs., to Kathleen M. Sanzo et al. 45 n.89 (May 30, 2006), available at <http://www.fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf>.

165. See Letter from Steven K. Galson, Dir., Ctr. for Drug Evaluation and Research, Dept. of Health and Human Servs., to Kathleen M. Sanzo et al., *supra* note 164, at 4 (noting usual scientific hurdles are not at issue with Omnitrope because it has single active ingredient, is well-characterized, and not glycosylated).

166. Katherine T. Adams, *Benefit Design: 10 Years, Still Shifting Gears*, BIOTECHNOLOGY HEALTHCARE, July–Aug. 2008, at 18, 23.

167. See FDA, SOPP 8401: ADMINISTRATIVE PROCESSING OF BIOLOGICS LICENSE APPLICATION (BLA) (2007), <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Procedures/SOPPs/ucm073074.htm> (explaining after 1999 amendment to PHSA that “[a]ll new marketing submissions for products subject to licensure under the PHS Act will be handled as BLAs or supplements to BLAs”).

168. See Arie M. Michelson, “Follow-On” Biologics: What Will It Take?, SCITECH LAW., Fall 2008, at 4, 4 (contrasting growth of biotechnology drug industry with absence of generic industry).

169. See *id.* at 8–9 (posing “major parameters of the debate” over follow-on biologics legislation).

170. See Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVS. DRUG DISCOVERY 479, 485–87 (2008) (providing break-even analysis for representative portfolio of biologics); BRILL, *supra* note 149, at 9 (estimating years until profitability for new biologics).

171. See Grabowski, *supra* note 170, at 487 (finding mean break-even product lifetime between 12.9 and 16.2 years).

172. BRILL, *supra* note 149, at 7–11. Brill contends that Grabowski’s use of the “break-even” point is flawed since profits will still be earned after generics enter the market. *Id.* at 4. Further he illustrates the wide range of results that are obtainable using the Grabowski model by employing other, reasonable discount rates. *Id.* at 8–9.

173. Letter from Robert Weissman, Dir., and Sarah Rimmington, Attorney, Essential Action, to Fed. Trade Comm’n (Dec. 22, 2008), available at http://www.essentialaction.org/access/uploads/Essential_Action_FTC_Comments_12.22.08.pdf.

174. Compare Access to Life-Saving Medicine Act, S. 623, 110th Cong. (2007) (granting no exclusivity period), with Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. § 2(a)(2)(k)(3)(C) (granting fifteen years with approval of new indication).

introduced two competing bills in March of 2009.¹⁷⁵ The Pathway for Biosimilars Act proposes a scheme granting the pioneer twelve years of exclusivity and the first FOB manufacturer two years.¹⁷⁶ It explicitly requires clinical studies investigating immunogenicity of the FOB product unless the requirement is waived.¹⁷⁷ A waiver may only be issued if the FDA publishes a final guidance determining “that it is feasible in the current state of scientific knowledge to make determinations on immunogenicity with respect to products in the product class to which the biological product belongs.”¹⁷⁸ A competing 2009 bill, the Promoting Innovation and Access to Life-Saving Medicine Act, grants pioneers five years of exclusivity and generally 180 days of exclusivity for the first FOB maker.¹⁷⁹

In March of 2010, legislation creating a biosimilar approval pathway was signed into law.¹⁸⁰ Entitled the Biologics Price Competition and Innovation Act of 2009 (“BPCIA”), the legislation was tucked into the sweeping health care overhaul.¹⁸¹ The BPCIA guarantees pioneer manufacturers at least twelve years of marketing exclusivity and the first biosimilar manufacture at least one year of marketing prior to the entry of a second biosimilar competitor.¹⁸²

C. *Compulsory Licensing and the Bayh-Dole Act*

Patent rights secure limited monopolies for individuals who create novel, useful, and nonobvious inventions.¹⁸³ The holder of a U.S. patent holds “the right to exclude others from making, using, offering for sale, or selling the invention”¹⁸⁴ for a term of twenty years from the date of filing.¹⁸⁵ The principal policy reason for granting limited monopolies is to encourage the creation and disclosure of innovations that will benefit the public.¹⁸⁶ Patent rights exist only under the enactment of Congressional legislation

175. For a succinct comparison of the bills’ essential features, see Gwilym Attwell et al., *Congress Considers Competing Biosimilars Legislation*, FISH & RICHARDSON—FISH NEWS, <http://www.fr.com/Congress-considers-competing-biosimilars-legislation/> (last visited Oct. 17, 2010).

176. Pathway for Biosimilars Act, H.R. 1548, 111th Cong. § 101(k)(6)–(7) (2009).

177. *Id.* §§ 101(a)(2)(k)(2)(A)(i)(III), (a)(2)(k)(2)(B)(ii).

178. *Id.* § 101(a)(2)(k)(2)(B)(ii)(I).

179. Promoting Innovation and Access to Life-Saving Medicine Act, H.R. 1427, 111th Cong. § 262(k)(10)–(11) (2009).

180. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001–03, 124 Stat. 119, 804–21 (2010).

181. *Id.* § 7001(a).

182. *Id.* § 7002(a)(2)(k)(6)–(7).

183. 35 U.S.C. §§ 101–103 (2006). When filing a patent, an applicant must also describe his invention in sufficient detail to enable another expert in his field to recreate the invention. *Id.* § 112. This is the “enablement” requirement. Section 112 also requires an applicant to disclose the best mode of practicing the invention and a sufficient written description of it. *Id.*

184. 35 U.S.C. § 154(a)(1).

185. *Id.* § 154(a)(2).

186. Rebecca S. Eisenberg, *Patents and the Progress of Science: Exclusive Rights and Experimental Use*, 56 U. CHI. L. REV. 1017, 1024 (1989).

and exist explicitly to incentivize scientific progress.¹⁸⁷ Congress may place limitations on patent rights of individuals such as categorizing certain subject matter as unpatentable¹⁸⁸ and determining that certain circumstances abrogate patent rights.¹⁸⁹

The owner of a patent can voluntarily license others to use the invention.¹⁹⁰ Under certain circumstances the government can make a license mandatory and grant a compulsory license.¹⁹¹ Generally the entity receiving the compulsory license must compensate the patent holder in exchange for the right to practice the invention.¹⁹² In the United States, relative to other developed countries, compulsory licensing is not a popular concept.¹⁹³ U.S. courts will on occasion apply compulsory licenses as a remedy in antitrust litigation.¹⁹⁴ Additionally, federal statutes explicitly permit compulsory licensing in limited circumstances.¹⁹⁵

187. The U.S. Constitution provides to Congress the power to “promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries.” U.S. CONST. art. 1, § 8, cl. 8.

188. Unpatentable subject matter includes laws of nature, natural phenomenon, and abstract ideas. *Gottschalk v. Benson*, 409 U.S. 63, 67 (1972).

189. For instance, where an inventor has kept his commercial process secret and sold the product for years, he cannot then acquire the protection of patent rights. *Metallizing Eng'g Co. v. Kenyon Bearing & Auto Parts Co.*, 153 F.2d 516, 520 (2d Cir. 1946).

190. See MARTIN J. ADELMAN ET AL., *CASES AND MATERIALS ON PATENT LAW* 1056–58 (2d ed. 2003) (defining license and distinguishing it from assignment of patent). “A license . . . is nothing more than a promise by the licensor not to sue the licensee, usually in exchange for the licensee’s promise to pay royalties.” *Id.* at 1058.

191. Pedro Roffe et al., *From Paris to Doha: The WTO Doha Declaration on the TRIPS Agreement and Public Health*, in *NEGOTIATING HEALTH: INTELLECTUAL PROPERTY AND ACCESS TO MEDICINES* 9, 14 (Pedro Roffe et al. eds., 2006) (defining compulsory license as “an authorization granted by a government to a party other than the holder of a patent on an invention to use that invention without the consent of the patent holder”).

192. See Colleen Chien, *Cheap Drugs at What Price to Innovation: Does the Compulsory Licensing of Pharmaceuticals Hurt Innovation?*, 18 *BERKELEY TECH. L.J.* 853, 859 (2003) (noting that amount of compensation is typically more than “reasonable royalt[ies]” but less than lost profits).

193. See World Trade Organization, Ministerial Declaration of 14 November 2001, WT/MIN(01)/DEC/1, 41 I.L.M. 746 (2002) (reaffirming stance taken in TRIPS allowing member states to compel licensing); Graham Dutfield, *Delivering Drugs to the Poor: Will the TRIPS Amendment Help?*, 34 *AM. J.L. & MED.* 107, 112 (2008) (generalizing that “[n]ational patent laws in Europe tend to provide for compulsory licensing and government use”). *But see* Copyright Act, 17 U.S.C. § 115(a) (2006) (explaining circumstances under which compulsory licenses for making and distributing phonorecords are available and detailing privileges associated with compulsory licenses).

194. *E.g.*, *United States v. Glaxo Group Ltd.*, 410 U.S. 52, 62–64 (1973); *Besser Mfg. Co. v. United States*, 343 U.S. 444, 447 (1952).

195. See Clean Air Act, 42 U.S.C. § 7608 (2006) (providing that if compliance with certain Clean Air Act provisions requires use of patent, district court may, after certification by Attorney General, issue order requiring patent owner to license it); Atomic Energy Act, 42 U.S.C. § 2183 (providing that Nuclear Regulatory Commission may declare patent to be “affected with the public interest” and may issue license on such patent); Plant Variety Protection Act, 7 U.S.C. § 2404 (2006) (providing that Secretary of Agriculture may declare protected variety open to wide usage if such declaration is necessary to ensure adequate public supply of food, fiber, or feed and owner is unwilling or unable to supply public need for the variety at reasonable price).

The Bayh-Dole Act empowers the government to compel licensing of patents obtained on federally funded inventions.¹⁹⁶ The Bayh-Dole Act was designed to encourage innovation by permitting small businesses, non-profits, and universities to patent inventions developed with federal assistance.¹⁹⁷ In exchange for giving the research entity patent rights, the government retains “march-in rights,”¹⁹⁸ permitting it to compel licensing.¹⁹⁹ The government can exercise its march-in rights by showing that the patent holder has failed to achieve a practical application of the invention or that licensing is necessary to address a public health concern.²⁰⁰

In 1994 CellPro asked the Secretary of the Department of Health and Human Services to use the government’s march-in rights and force John Hopkins University to license unexploited patents.²⁰¹ The Secretary delegated the power to evaluate CellPro’s request to The National Institutes of Health (“NIH”). The NIH reviewed and refused the request.²⁰² In fact, the government has never exercised its march-in rights, leaving the compulsory licensing provision of the Bayh-Dole Act essentially dormant.²⁰³ Notably, only two petitions have been filed since the CellPro petition. Two unrelated 2004 petitions claimed that the government should exercise march-in rights in order to alleviate inflated prices.²⁰⁴ Responding to one of these petitions, the NIH Director wrote that “the NIH believes that the extraordinary remedy of march-in is not an appropriate means of controlling prices” and deferred that power to Congress.²⁰⁵ Thus,

196. Bayh-Dole Act, 35 U.S.C. §§ 200–212 (2006). Under § 201(b), federal funding is defined as “any contract, grant, or cooperative agreement entered into between any Federal agency . . . and any contractor for the performance of experimental, developmental, or research work funded in whole or in part by the Federal Government.” *Id.* § 201(b).

197. *Id.* § 202.

198. *Id.* § 203. See generally John H. Raubitschek & Norman J. Latker, *Reasonable Pricing—A New Twist for March-In Rights Under the Bayh-Dole Act*, 22 SANTA CLARA COMPUTER & HIGH TECH. L.J. 149 (2005). The term “march-in rights” dates back at least to the middle of the twentieth century and describes the reserved right of the government to exert ownership over inventions it funded. *Id.* at 151–52.

199. HOWARD BRODY, *HOOKED: ETHICS, THE MEDICAL PROFESSION, AND THE PHARMACEUTICAL INDUSTRY* 78 (2007).

200. 35 U.S.C. § 203(a).

201. Peter Mikhail, Note, *Hopkins v. CellPro: An Illustration That Patenting and Exclusive Licensing of Fundamental Science Is Not Always in the Public Interest*, 13 HARV. J.L. & TECH 375, 387–88 (2000). Hopkins sued CellPro for infringing patented technology it developed using NIH funding. *Id.* at 386–87. CellPro was marketing a cancer treatment tool that utilized the technology. *Id.* at 385–86. Neither Hopkins nor its exclusive licensee had yet developed a competing product, and CellPro argued enforcing the patent would leave a public health need unmet. *Id.* at 386–87.

202. Press Release, Nat’l Insts. of Health, Determination in the Case of Petition of CellPro, Inc., <http://www.nih.gov/news/pr/aug97/nihb-01.htm> (last visited Oct. 30, 2010).

203. U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-09-742, INFORMATION ON THE GOVERNMENT’S RIGHT TO ASSERT OWNERSHIP CONTROL OVER FEDERALLY FUNDED INVENTIONS 9 (2009), available at <http://www.gao.gov/products/GAO-09-742>. Rai and Eisenberg hypothesize that procedural obstacles partially explain the reluctance of the NIH to initiate proceedings. See Arti K. Rai & Rebecca S. Eisenberg, *Bayh-Dole Reform and the Progress of Biomedicine*, 66 LAW & CONTEMP. PROBS., Winter/Spring 2003, at 289, 294.

204. U.S. GOV’T ACCOUNTABILITY OFFICE, *supra* note 203, at 11.

205. ELIAS A. ZERHOUNI, NAT’L INSTS. OF HEALTH, IN THE CASE OF XALATAN MANUFACTURED BY PFIZER (Sept. 17, 2004), available at <http://ott.od.nih.gov/policy/March-in-xalatan.pdf>. The NIH’s position, that drug pricing is the providence of Congress alone, is reiterated in a 2001 report: A Plan to Ensure Taxpayers’ Interests Are Protected, available at <http://www.nih.gov/news/070101wyden.htm>.

the NIH construes Bayh-Dole's compulsory licensing provision narrowly, precluding its use as an avenue to lower drug prices and increase access.

III. DISCUSSION

As part of a biosimilars approval pathway, Congress should have explicitly permitted the compulsory licensing of any intellectual property necessary to produce monoclonal antibody therapies and other highly complex drugs once a reasonable exclusivity period expires.²⁰⁶ The two paramount concerns with biosimilar antibody drugs are ensuring safety and ensuring that the treatments become available at reasonable prices once the pioneer manufacturer earns a sufficient profit. As science and FDA requirements now stand, no follow-on antibody product will go to market without evaluation in clinical trials to ensure safety and efficacy.²⁰⁷ The extent, and accordingly the cost, of these trials can be reduced if the entities owning the required intellectual property license it. With lower entry costs, more follow-on manufacturers will be able to enter the market in less time.²⁰⁸ Pioneers will still earn a sufficient profit to encourage innovation through a reasonable exclusivity period and subsequently through licensing fees for the life of the patent.²⁰⁹ The incentive to invent will remain, but the ability to hold a perpetual monopoly while charging patients, health care providers, and government assistance programs astronomical prices will be lost. Monoclonal antibodies are a significantly different type of drug, and the FDA approval system must make significant adjustments to strike the right balance between industry and consumer interests.

A. *The Reality and Repercussions of FDA Standards Applied to Antibody Therapies*

1. Follow-On Antibody Drugs Will Require New Clinical Trial Data: Hatch-Waxman Part Two Is Not a Sufficient Solution

The heart of Hatch-Waxman is the premise that a generic drug manufacturer need not prove the safety and efficacy of a product if it proves that the product is pharmaceutically identical and bioequivalent to an approved drug.²¹⁰ This premise allows generic drug makers to bypass hundreds of millions of dollars in clinical trial costs.²¹¹ Hatch-Waxman assumes that if clinical trials demonstrated that pioneer drug A is safe and effective and generic drug B is pharmaceutically equivalent and

206. See *infra* Part III.B for arguments supporting this contention.

207. See *infra* Part III.A.1 for the argument that clinical trial demands and costs will be significant for antibody drugs.

208. See *infra* Part III.A.3 for an explanation of how high licensing costs disincentivize follow-on manufacturers.

209. See *infra* Part III.B.1 for a discussion of the benefits of licensing for the pioneer manufacturers.

210. Mossinghoff, *supra* note 152, at 190–91.

211. See Gitter, *supra* note 128, at 571 (reporting that full NDA costs total around 800 million dollars while bringing generic to market costs only around one or two million).

bioequivalent to drug A, then drug A trials establish drug B is safe and effective.²¹² The nature of small-molecule drugs makes this a safe inference.²¹³ However, at our current state of technology, the very different nature of monoclonal antibodies prevents an analogous inference from being confidently made.²¹⁴ Accordingly, the FDA is unlikely to allow a follow-on manufacturer of a monoclonal antibody to market a treatment without conducting clinical trials.²¹⁵ The need for millions of dollars of clinical trials for a follow-on application strikes at the heart of the theory of an abbreviated pathway.²¹⁶ The pathway will not be quick, it will not be cheap, and if these novel conditions are not accounted for, it will not create a competitive therapeutic antibody market.²¹⁷

The distinguishing factors between drugs regulated under Hatch-Waxman and therapeutic antibodies are the complexity, stability, and predictability of the molecules, and the ability of modern science to characterize the products.²¹⁸ Generally, small-molecule pharmaceuticals are stable, homogenous compositions.²¹⁹ The production process is a stepwise synthesis applying tried and true techniques.²²⁰ Small-molecule drugs can be characterized to ensure the safety and uniformity of what will enter patient's bodies.²²¹ Thus, reliable scientific methods provide the FDA with evidence

212. See Mossinghoff, *supra* note 152, at 190–91 (noting Hatch-Waxman Act made two major assumptions: (1) “that duplicates of pioneer drugs would be the same as the innovator’s drug” and (2) “that bioequivalence data was an effective surrogate for safety and efficacy”).

213. FDA, Generic Drugs: Questions and Answers, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm> (last visited Oct. 30, 2010).

214. Schneider & Kalinke, *supra* note 23, at 988; see also Sitte, *supra* note 92, at 37 (comparing ability to create generic small-molecule drugs with ability to develop biosimilar treatments and noting that properties of biologics “render predictions on their physicochemical and biological, thus, clinical effects difficult to impossible”).

215. Grabowski et al., *supra* note 127, at 442; see also *Follow-On Biologics: Hearing of the S. Comm. on Health, Educ., Labor, and Pensions*, 110th Cong. 14–26 (2007) [hereinafter *Hearing*] (statement of Jay P. Siegel, Group President of Research and Development for Biotechnology, Immunology, and Oncology, Johnson & Johnson), available at <http://docs.govdoc.org/us/legi/senate/chelp/hearings/SHRG-110-0375.pdf> (arguing that complexity and inability to characterize biologics determines that pre-market clinical testing will be necessary); David M. Dudzinski & Aaron S. Kesselheim, *Scientific and Legal Viability of Follow-On Protein Drugs*, 358 NEW ENG. J. MED 843, 847 (2008).

216. See Dudzinski, *supra* note 13, at 232 (arguing that requiring repeated rounds of clinical trials for generic biologics may be tantamount to having no abbreviated pathway to approval and may eventually undermine notion of generic biologics altogether).

217. See *infra* Part III.A.3 for the argument that a competitive market will fail to develop.

218. See *supra* Part I for an explanation of the basic distinctions between the two drug categories.

219. See *Hearing*, *supra* note 215, at 17 (describing them as “relatively small, relatively simple in structure, and relatively easy to replicate using carefully controlled processes. . . . [allowing for] precise characterization and detection of even minor changes in the product”).

220. See Dudzinski, *supra* note 13, at 155 (explaining that success of small-molecule paradigm reflects relative simplicity of molecules and reliability with which different experts can produce them in different places and yield identical products).

221. See *id.* (“With . . . a perfectly identifiable and (nearly) perfectly homogenous small molecule, biochemical assays and clinical trials [can] be performed in order to measure the molecule’s specific effects as well as toxicities.”).

that generic drugs are bioequivalent to pioneer drugs without a new set of lengthy and expensive clinical trials.²²²

In contrast, experts cannot assume a complex follow-on biologic is identical to the reference drug.²²³ Since they cannot be “the same,” academics and legislators do not call them generics, but biosimilars and follow-on biologics. The question becomes then, how different are they? Is the follow-on product similar enough that its safety and efficacy can be assumed? Can one infer that follow-on product B will behave in clinical trials the same as pioneer product A? For many small, less complex follow-on biologics, the inference of bioequivalence is possible.²²⁴ However, antibodies are exceptionally large, complex molecules with large-scale production procedures fraught with the potential for errors and inconsistencies.²²⁵ They can aggregate, unfold, or otherwise act unpredictably.²²⁶ Bioreactor conditions and purification steps must be “highly reproducible” for anything close to the desired product to result.²²⁷

These production issues equate to significant safety and efficacy issues.²²⁸ The safety-related regulatory actions already taken for monoclonal antibodies on the market demonstrate the cause for concern.²²⁹ Out of fifteen humanized monoclonal antibodies approved in the United States and Europe, there were eleven safety-related regulatory actions taken.²³⁰ There have also been clinical trial incidents of unexpected severity. In one phase I study the six healthy individuals receiving their first dose of antibody ended up in intensive care suffering multiple organ failures among other infirmities.²³¹

Methods exist to assess the immunogenicity profile of proteins, but experts assert that they cannot actually predict how patients will react.²³² Recent scholarship pointed out that “critical gaps” are present in the current therapeutic protein evaluation protocols meant to analyze the presence of a key immunogenicity risk factor.²³³ “Only relevant clinical experience, which encompasses both clinical trials and post-marketing surveillance (pharmacovigilance), [can] guarantee the safe behavior of the protein in patients.”²³⁴

222. FDA, *supra* note 213.

223. Cormac Sheridan, *First Generic Biologics Finally Approved*, 5 NATURE REVS. DRUG DISCOVERY 445, 445 (2006).

224. See *supra* Part II.B.2 for a discussion of copycat biologic drugs that have received abbreviated approval.

225. See *supra* Part II.A.3 for a discussion of the hurdles to manufacturing a biosimilar product.

226. Schneider & Kalinke, *supra* note 23, at 988.

227. Carson, *supra* note 103, at 1057.

228. See *supra* Part II.A.3 for a discussion of the safety concerns implicated by commercial manufacture of therapeutic monoclonal antibodies.

229. Thijs J. Giezen et al., *Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union*, 300 J. AM. MED. ASS'N 1887, 1888 (2008).

230. *Id.* at 1893.

231. Ganesh Suntharalingam et al., *Cytokine Storm in a Phase I Trial of the Anti-CD28 Monoclonal Antibody TGN1412*, 355 NEW ENG. J. MED. 1018, 1018–19 (2006).

232. Trouvin, *supra* note 108, at 308.

233. Carpenter et al., *supra* note 96, at 1203–04.

234. Trouvin, *supra* note 108, at 308.

Prior approval actions of the FDA also suggest that clinical trials will be necessary for mAb therapies. In April 2008 the FDA rejected approval sought by Genzyme to manufacture its biologic drug Myozyme at a different scale in a new plant.²³⁵ The only practical difference anticipated was the glycosylation of the molecule.²³⁶ The FDA found the difference necessitated that Genzyme file a completely new BLA.²³⁷

The exact requirements the FDA will issue to ensure the safety and efficacy of follow-on antibody drugs remain unknown, but they are likely to be demanding.²³⁸ FDA guidance on manufacturing changes like those proposed by Genzyme provides some insight. It lists the expected techniques a manufacturer will use to characterize the product.²³⁹ Most importantly, it emphasizes that nonclinical or clinical studies are necessary when the manufacturer lacks evidence that efficacy or safety will not be impacted by the proposed changes.²⁴⁰ The Biologics Price Competition and Innovation Act of 2009 makes clinical trials investigating immunogenicity an explicit requirement.²⁴¹ Even if only a single phase III trial were required with a reduced number of subjects, it would cost millions of dollars.²⁴² “Requiring substantial clinical trials as part of an abbreviated biologics approval pathway may be tantamount to having no abbreviated pathway at all, eviscerating any notion of generic biologics”²⁴³

235. *Genzyme Provides Update on Myozyme® Manufacturing*, FIERCEBIOTECH (Apr. 21, 2008), available at <http://www.fiercebiotech.com/press-releases/genzyme-provides-update-myozyme-manufacturing>.

236. *See id.* (noting production of Myozyme at higher scale required additional approval because of differences in molecules' carbohydrate structures at higher scale).

237. *Id.*

238. Although Congress has enacted follow-on biologics legislation, the specifics of the approval process will be determined by the FDA. *See FDA, Implementation of the Biologics Price Competition and Innovation Act of 2009*, *supra* note 20. Congress left it to the discretion of the FDA whether it will issue class-specific guidance and make requirements more demanding for certain classes of products like monoclonal antibody drugs. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002(a)(2)(k)(8)(D), 124 Stat. 119, 808 (2010).

239. FDA, ICH Q5E: COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS ¶ 2.2.2 (2003), available at <http://www.fda.gov/OHRMS/DOCKETS/98fr/2004d-0118-gd10001.pdf>. The guidance requires “[c]haracterisation of a biotechnological/biological product by appropriate techniques . . . includ[ing] the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants, and quantity.” *Id.*

240. *Id.* ¶ 3.0.

241. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002(a)(2)(k)(A)(i)(I)(cc), 124 Stat. 119, 805 (2010).

242. Grabowski et al., *supra* note 127, at 442.

243. Dudzinski, *supra* note 13, at 232.

2. Beyond Clinical Trials: Additional Costs Faced by Follow-On Manufacturers

The physical process of making a biologic drug is more involved and much more costly than making a small-molecule drug.²⁴⁴ Adequate manufacturing facilities are a serious concern.²⁴⁵ Generally, “antibody therapies require high doses over a long period of time, which requires large amounts of purified product per patient.”²⁴⁶ Building a multiproduct manufacturing plant can cost upwards of \$250 million and take three to five years to get operational.²⁴⁷ Contract manufacturing is an option, but this method comes with its own costs and risks.²⁴⁸

Also, many experts remain skeptical that any FOB could be classified as “interchangeable.”²⁴⁹ A designation of interchangeability is paramount to generic profitability. If physicians and pharmacists are not free to switch patients to the follow-on product at their discretion, then the biosimilar will not quickly grab market share. Physicians themselves may also be reluctant to make the switch to a biosimilar.²⁵⁰

3. High Costs for FOB Manufacturers Will Inhibit a Competitive Market

If manufacturing costs are high and significant clinical trials are required, bringing a follow-on antibody drug to market could cost up to \$200 million.²⁵¹ As the costs for entering the market increase, the number of follow-on entrants will decrease.²⁵² Monopolies or near-monopolies on blockbuster treatments will persist along with sky-high prices.²⁵³ The public will receive the benefit of increased innovation in the form of novel treatments, and the innovators will recoup their costs plus a hefty profit. However, how many patients will these drugs reach if costs stay as they are or escalate

244. See Sommerfeld & Strube, *supra* note 40, at 1126 (reporting that small-molecule drugs generally cost less than five dollars per gram to produce compared to one hundred to one thousand dollars per gram for protein therapies); Pollack, *supra* note 10 (reporting that complexity of biotechnology protein drugs insulates companies that make them from generic competition, unlike in case of typical drug).

245. See Wang, *supra* note 1, at B3 (pointing out importance of Eli Lilly’s acquisition of ImClone’s biologics facilities).

246. Feng Li et al., *supra* note 73, at 1.

247. Grabowski, *supra* note 170, at 483 box 3, n.2.

248. See Carson, *supra* note 103, at 1055 (warning that contract facilities result in reduced control of process and increase contamination risks).

249. See Pamela Jones Harbour, Comm’r, Fed. Trade Comm’n, Remarks at Biosimilars 2008: The Federal Trade Commission’s Perspective on Biosimilars: Current Initiatives and Long-Term Goals 8 (Sept. 23, 2008) (transcript available at <http://www.ftc.gov/speeches/harbour/080923biosimilars.pdf>) (discussing possibility of less market competition under biologics legislation than under Hatch-Waxman because of inability to deem biologics “interchangeable”); Behrman, *supra* note 21, at 16–18 (explaining that, unlike with ordinary generic drugs, current technology does not permit assumption that active ingredients in follow-on biologics are interchangeable with ingredients in original biologics).

250. Chester G. Moore, *Generic Biologic Drugs: What’s in a Name?*, SCITECH LAW., Fall 2008, at 16, 18.

251. See Grabowski et al., *supra* note 127, at 443 (estimating a range of two to two hundred million dollars).

252. *Id.* at 445.

253. See *id.* at 440 (explaining scenario with only two follow-on biologics entrants would result in their products being priced at eighty-two percent of the branded product).

further?²⁵⁴ Researchers have already published a flurry of papers providing cost-benefit analyses of specific biologic therapies compared to more traditional treatment regimes.²⁵⁵

B. Compulsory Licensing: A Solution to Increase Market Competition and Product Safety

1. The Need for Licensing and Data Sharing in the Complex Biologics Market

Follow-on biologics bills included exclusivity grants to brand manufacturers ranging from zero to fourteen years.²⁵⁶ Why the cavernous disconnect? Because there is no magic exclusivity number to solve the problem. The monoclonal antibody market generates a more complex problem than simply balancing innovation incentives and public access through the correct exclusivity grant.²⁵⁷ Rather, this novel problem requires a novel solution which takes into account its unique features: (1) significant safety concerns, (2) prohibitively high market-entry costs, and (3) the need to avoid permitting and incentivizing perpetual monopolies.

Coupling a reasonable exclusivity period with the possibility of compulsory licensing and data-sharing incentives is a solution which addresses the different facets of the FOB problem. In situations where a treatment is too complex for the FDA to allow a truly abbreviated approval,²⁵⁸ the government should have the power to compel licensing and data disclosures. These disclosures would include the patents and clinical trial data submitted to obtain the NDA.²⁵⁹ Additionally, the first-to-file FOB manufacturer should receive an exclusivity period for agreeing to share its

254. See Laurence J. Kotlikoff, Op-Ed., *Clearing the Way for Low-Cost Biogenerics*, BOSTON GLOBE, Oct. 26, 2008, at D9 (suggesting that biologic drugs are already unreachable for forty-seven million uninsured Americans and are heading that way for others unable to afford escalating co-pays).

255. E.g., Quan V. Doan et al., *Review of Eight Pharmacoeconomic Studies of the Value of Biologic DMARDs (Adalimumab, Etanercept, and Infliximab) in the Management of Rheumatoid Arthritis*, 12 J. MANAGED CARE PHARMACY 555, 559–60 (2006); Andrew A. Nelson et al., *Cost-Effectiveness of Biologic Treatments for Psoriasis Based on Subjective and Objective Efficacy Measures Assessed over a 12-Week Treatment Period*, 58 J. AM. ACAD. DERMATOLOGY 125 (2008).

256. *Compare Access to Life-Saving Medicine Act*, S. 623, 110th Cong. (2007) (granting no exclusivity period), with *Patient Protection and Innovative Biologic Medicines Act of 2007*, H.R. 1956, 110th Cong. § 2(a)(3)(B) (granting fourteen years).

257. This is the traditional, persisting model. See Meir Perez Pugatch, *Intellectual Property, Data Exclusivity, Innovation and Market Access*, in NEGOTIATING HEALTH: INTELLECTUAL PROPERTY AND ACCESS TO MEDICINES, *supra* note 191, at 97, 98 (describing that patent exclusivity involves balancing “two basic social needs”).

258. See Schneider & Kalinke, *supra* note 23, at 990 (expressing doubt that biosimilar pathway will be feasible for all monoclonal antibody drugs).

259. Compelling licensing of the complete clinical trial data is vital to reducing FOB maker costs and increasing the safety of subsequent trials. See Aaron Bouchie, *Clinical Trial Data: To Disclose or Not to Disclose?*, 24 NATURE BIOTECHNOLOGY 1058, 1060 (2006) (discussing the reduced cost and safety benefits of sharing phase 1 study data); Dudzinski, *supra* note 13, at 234 (arguing clinical trials for generic biologics would raise costs of development).

manufacturing knowledge and to deposit its cell line at a centralized cell bank.²⁶⁰ The first FOB maker would get six months to a year of exclusivity, and subsequent entrants would receive some of the fruits of their R&D dollars. While unorthodox, the advantages of a system employing compulsory licensing and data-sharing mechanisms are significant.

Compulsory licensing of the patents provides economic advantages for both the pioneer and the FOB manufacturers. When the biosimilar product enters the market, unlike under Hatch-Waxman, the pioneer drug maker will not automatically see profits plummet.²⁶¹ Rather, the innovator will make money from each biosimilar dose sold, in the form of licensing revenue.²⁶² Encouraging licensing instead of paragraph IV-type litigation could also relieve brand manufacturers of defending against increasingly routine and protracted suits.²⁶³

For FOB manufacturers, licensing and data-sharing mechanisms will decrease the costs of bringing a product to market. Access to the BLA data will save FOB manufacturers time and money in designing clinical trials and optimizing product production.²⁶⁴ It would allow follow-on manufactures to learn from the innovator's methodology and to avoid repeating mistakes.²⁶⁵ A license on the patented invention(s) would increase the productivity of the entire industry,²⁶⁶ because it would give FOB makers a more efficient option than designing around the branded drug's patents.²⁶⁷

260. A cell bank is a repository of biological material and related information. Tom Dedeurwaerdere, *The Institutional Dynamics of Sharing Biological Information: Towards Reflexive Governance of the Information Society*, in *THE INFORMATION SOCIETY: INNOVATION, LEGITIMACY, ETHICS AND DEMOCRACY* 121, 125 (Philippe Goujon et al. eds., 2007). An example of such a system is the European Searchable Tumour Line Database, a database of cell lines linking to a cell bank which sends cells to researchers. James Robinson et al., *The European Searchable Tumour Line Database*, 58 *CANCER IMMUNOLOGY, IMMUNOTHERAPY* 1501 (2009).

261. See Glass, *supra* note 158, at 953 (estimating eighty percent of market can be captured by generic only fifteen to twenty percent cheaper); Matthew Avery, Note, *Continuing Abuse of the Hatch-Waxman Act by Pharmaceutical Patent Holders and the Failure of the 2003 Amendments*, 60 *HASTINGS L.J.* 171, 172 (2008) (reporting that once generic entry occurs, pioneer can lose eighty to ninety percent of its market).

262. The innovator could set the royalty rate, subject to judicial oversight or an arbitration procedure.

263. See Henry Grabowski, *Are the Economics of Pharmaceutical Research and Development Changing?: Productivity, Patents and Political Pressures*, 22 (Supp. 2) *PHARMACOECONOMICS* 15, 19–21 (2004) (reporting sharp increase in paragraph IV litigation since 1992).

264. Under the proposed scheme, data would be shared regardless of any patents or trade secret claims. Bouchie, *supra* note 259, at 1060.

265. See *id.* (reporting opinions of experts that clinical trial information sharing would be efficient solution for the industry).

266. U.S. DEP'T OF JUSTICE & FED. TRADE COMM'N, *ANTITRUST GUIDELINES FOR THE LICENSING OF INTELLECTUAL PROPERTY* 4–6 (1995), available at <http://www.justice.gov/atr/public/guidelines/0558.pdf>.

267. This way, five manufacturers will not spend a decade designing five different ways to target the same protein. An example of this is Merck's recently disclosed BioVentures division and its long-term plan to produce follow-on biologics that design around pioneer manufacturers' patents. Rockoff & Winslow, *supra* note 74, at B1.

While multiplicity leads to innovation in certain instances,²⁶⁸ it is often a waste of resources.²⁶⁹

Finally, Congress should have included compulsory licensing and data-sharing mechanisms in follow-on biologics legislation because they will benefit the public. In general, data sharing increases research efficiency by allowing for increased access to information and collaboration.²⁷⁰ With respect to clinical trials, safety concerns and ethical issues are leading to louder calls for data sharing.²⁷¹ In 2007 Congress enacted legislation expanding mandatory registration of clinical trials, demonstrating a commitment to increasing safety and accountability.²⁷² Current requirements do not go far enough because they do not mandate complete disclosure of methods and results.²⁷³ Sharing complete information increases the safety of future trials by reducing the chance of repeating errors.²⁷⁴ Pioneers contend clinical trial data is protected by trade secret law.²⁷⁵ However, the data should be treated as an essential part of the quid pro quo for receiving marketing approval and exclusivity. Just as a patent applicant provides an enabling disclosure in exchange for a limited monopoly,²⁷⁶ a pioneer should be required to exchange enabling clinical trial data for temporary market exclusivity. Pioneers would probably resist sharing manufacturing know-how and physical cell lines even more strongly.²⁷⁷ Thus, these components should be acquired by incentivizing the first follow-on manufacturer to provide them.

268. See Nils Lonberg, *Fully Human Antibodies from Transgenic Mouse and Phage Display Platforms*, 20 CURRENT OPINION IN IMMUNOLOGY 450, 453 (2008) (discussing approval of panitumumab, a fully human antibody that targets same receptor as the Eli Lilly drug, and reporting its better safety profile).

269. An article reviewing antibody engineering technology noted that “the multiplicity of engineered mAbs” is “driven in part by the desire to circumvent intellectual property complications.” Leonard G. Presta, *Engineering of Therapeutic Antibodies to Minimize Immunogenicity and Optimize Function*, 58 ADVANCED DRUG DELIVERY REVS. 640, 641 (2006).

270. See, e.g., Dov Greenbaum & Mark Gerstein, *A Universal Legal Framework as a Prerequisite for Database Interoperability*, 21 NATURE BIOTECHNOLOGY 979, 979, 981–82 (2003) (discussing importance of scientific databases and suggesting compulsory licensing as method of increasing access).

271. See generally Deborah A. Zarin & Tony Tse, *Moving Toward Transparency of Clinical Trials*, 319 SCIENCE 1340 (2008). In January 2008 the NIH began requiring that any genome-wide association study it funds must contribute to a central data bank. NAT'L INSTS. OF HEALTH, POLICY FOR SHARING OF DATA OBTAINED IN NIH SUPPORTED OR CONDUCTED GENOME-WIDE ASSOCIATION STUDIES (GWAS) (2007), available at <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-07-088.html#rational>. The researchers must submit the methodology as well as the results of their study. *Id.*

272. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, sec. 801, § 402, 121 Stat. 823, 904.

273. See Zarin & Tse, *supra* note 271, at 1342 (emphasizing areas where lack of transparency persists).

274. See Tjalf Ziemssen, *What Can We Learn from Failed Clinical Trials in Multiple Sclerosis?*, 255 (Supp. 6) J. NEUROLOGY, Dec. 2008, at 97, 97–98 (arguing for increased disclosure because “negative trials can provide valuable information about study design and outcome measures for future trials”).

275. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL'Y L. & ETHICS 717, 736–39 (2005).

276. See *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1344 (Fed. Cir. 2005) (discussing requirements for patent specification).

277. See Zarin & Tse, *supra* note 271, at 1342 (noting innovator concerns over intellectual property).

Ideally this scheme would lead to two or more biosimilars entering the market, creating true competition and more affordable, safer treatments for patients.²⁷⁸

2. Legal Grounds to Compel Licensing and Encourage Data Disclosures

Applying the premises of the march-in rights granted by the Bayh-Dole Act demonstrates that compulsory licensing in the context of federally funded monoclonal antibody therapies is a legally sound and expedient solution.

i. Whose Intellectual Property Is It Anyway?

Drugs are generally protected by multiple concurrent forms of intellectual property protection. First, they are protected by patents. Patents may cover the compound itself as well as the process used to make the compound. Second is marketing exclusivity. Hatch-Waxman provides five years of marketing exclusivity for small-molecule drugs.²⁷⁹ This ensures that even if the patent(s) covering the drug are invalidated or will expire shortly after approval, the pioneer has a fair chance to recover its investment. Third, drug manufacturers may claim intellectual property in their trade secrets. Compulsory licensing only relates to the patents protecting a drug, so it would not affect the exclusivity periods.

The patent-law landscape for biologics is highly complex, reflective of the products themselves. Following the Supreme Court's landmark decision in *Diamond v. Chakrabarty*,²⁸⁰ the scope of patentable subject matter has continued to expand, engulfing biotechnology advances as they arose.²⁸¹ For any given antibody therapy, there will likely be multiple layers of patent protection.²⁸² Separate patents will claim the drug target,²⁸³ technologies used to develop a therapy specific to the target,²⁸⁴ the process of manufacturing the therapy,²⁸⁵ and the therapeutic product itself.²⁸⁶

Further confusing the situation, certain types of patents are generally held by universities or third-party companies rather than the biologic manufacturer itself.²⁸⁷

278. See Grabowski et al., *supra* note 127, at 440 (noting that only entry of multiple generic manufacturers will significantly lower prices).

279. See *supra* Part II.B.2 for an explanation of Hatch-Waxman marketing exclusivity.

280. 447 U.S. 303 (1980) (finding transgenic bacteria is patentable subject matter).

281. Though a breadth of biotech advances is patentable, the federal circuit has created limits. See *Brenner v. Manson*, 383 U.S. 519, 534–37 (1966) (articulating more demanding utility test for biotech inventions and invalidating process patent for making steroid with no known applications); *In re Fisher*, 421 F.3d 1365, 1370–79 (Fed. Cir. 2005) (invalidating patent for expressed sequence tags based on application of “substantial and specific utility” standard).

282. See Rochelle Seide, Remarks at FTC Roundtable, *supra* note 21, at 216–17 (discussing “tiers” of patents existing on hypothetical biologic).

283. See *id.* at 217–18 (characterizing them as basic science patents owned by university researchers).

284. See *id.* at 219 (characterizing “technology platform patents” as owned by third-party companies).

285. See *id.* at 220 (providing examples of process patents owned by biologic manufacturer).

286. See *id.* (providing example of a “masked recombinant antibody,” the therapeutic antibody that has been humanized for reduced immunogenicity); see also KENNETH J. BURCHFIEL, BIOTECHNOLOGY AND THE FEDERAL CIRCUIT 23–24 (1995) (describing biotechnology product claims).

287. See Rochelle Seide, Remarks at FTC Roundtable, *supra* note 21, at 217–21 (discussing in hypothetical which patents would likely be held by universities).

After the Bayh-Dole Act initiated the “massive surge in university patenting,”²⁸⁸ a corollary increase in public-private ventures followed.²⁸⁹ A system developed where universities use federal money to make and patent basic science discoveries and then routinely license the technology to biotechnology companies.²⁹⁰ “Upstream” inventions²⁹¹ are exclusively licensed for development as “downstream” products.²⁹² Exclusive licensing agreements are the standard because they return maximum profits.²⁹³ In 2000 alone, universities earned \$1.26 billion in licensing revenue.²⁹⁴ Although there may be half a dozen patents necessary to the manufacturing process of a given biologic therapy, few are owned and enforced by the manufacturer.²⁹⁵ Thus, many of the patents protecting biologics are not even owned by innovator drug companies. The companies themselves are the licensees.

The Bayh-Dole Act has made it difficult to draw the line between public and private research.²⁹⁶ U.S. taxpayers spend more than \$20 billion each year on health-related research, making the American public the country’s number-one pharmaceutical investor.²⁹⁷ In the case of monoclonal antibody therapies, the government has frequently financed the development of the technology, consistently at the basic science level and often beyond. The NIH has and continues to contribute significantly to the development of therapeutic monoclonal antibodies destined for private intellectual property rights.²⁹⁸ In recent years grants have been awarded to such projects as “A

288. Mark A. Lemley, *Are Universities Patent Trolls?*, 18 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 611, 614–15 (2008); see also Ron A. Bouchard, *Balancing Public and Private Interests in the Commercialization of Publicly Funded Medical Research: Is There a Role for Compulsory Government Royalty Fees?*, 13 B.U. J. SCI. & TECH. L. 120, 121–22 (2007) (listing Bayh-Dole Act as one of the “events [that] spawned the global biotechnology revolution”); Lemley, *supra*, at 614–15 (noting that universities control eighteen percent of biotechnology patents as compared to one percent of all patents in all fields).

289. See Caroline A. Crenshaw, Note, *Patents and Patients: Who Is the Tragedy of the Anticommons Impacting and Who Is Bearing the Cost of High-Priced Biotechnological Research?*, 9 MINN. J.L. SCI. & TECH. 913, 917–18 (2008) (discussing increase in public-private joint ventures following Bayh-Dole Act).

290. See generally Risa L. Lieberwitz, *Confronting the Privatization and Commercialization of Academic Research: An Analysis of Social Implications at the Local, National, and Global Levels*, 12 IND. J. GLOBAL LEGAL STUD. 109 (2005).

291. Upstream patents can be defined as “patents that claim technologies associated with basic and early stage research and development, as opposed to patents covering ‘downstream’ commercial products.” Chris Holman, *Clearing a Path Through the Patent Thicket*, 125 CELL 629, 629 (2006).

292. *Id.*

293. See Mark A. Lemley, *Patenting Nanotechnology*, 58 STAN. L. REV. 601, 626–27 (2005) (explaining why universities choose to grant exclusive rather than nonexclusive licenses).

294. See Michael J. Shuster et al., *Protecting Rights to Early-Stage Technology*, 21 NATURE BIOTECHNOLOGY 701, 701 (2003) (discussing universities’ increase in revenue generated by research licensing).

295. See *id.* (discussing multiple patent claims that one biologic may have while on course to commercialization).

296. David E. Adelman, *A Fallacy of the Commons in Biotech Patent Policy*, 20 BERKELEY TECH. L.J. 985, 989 (2005).

297. Peter Arno & Michael Davis, Editorial, *Paying Twice for the Same Drugs*, WASH. POST, Mar. 27, 2002, at A21.

298. For instance, in 2006, the NIH provided a two million dollar grant to AVANIR Pharmaceuticals for its animal trials of an antibody targeted to inhaled anthrax. *AVANIR Pharmaceuticals Awarded \$2 Million NIH Grant to Continue Development of Human Antibody to Anthrax Toxin*, BUS. WIRE, June 30, 2006,

Novel Therapeutic Antibody for Treatment of Ischemic Stroke” (awarded to Avantgen, Inc.), “Development of a Novel Method for Inhibiting Atherosclerosis in Diabetes” (awarded to Vascular Pharmaceuticals), “Monoclonal Antibodies for Alzheimer’s Immunotherapy” (awarded to Mapp Biopharmaceutical, Inc.).²⁹⁹

The federal government has supported monoclonal antibody therapy research to serve public health needs. Thus, the government retains an interest in ensuring that those therapies become a reality and are available on reasonable terms to the public.

ii. Justifying Intervention: Reasonable Availability and Public Health Concerns

The Bayh-Dole Act permits the government to exercise compulsory licensing power if an invention is not reasonably available to the public or if licensing will resolve an unmet health need.³⁰⁰ Some argue that Bayh-Dole was meant to permit the government to license unreasonably priced drugs to manufacturers willing to provide consumers with reasonably priced medications.³⁰¹ Supporting this interpretation, a stated policy objective of the Act is to “protect the public against nonuse or unreasonable use of inventions.”³⁰² On the contrary, the NIH takes the position that a health need is reasonably satisfied if a safe and effective treatment is available on the open market.³⁰³ The NIH also makes clear that its position is based at least in part on deference to Congress as pricing issues should be dealt with directly through legislation. Congress should take the NIH up on this invitation.

http://findarticles.com/p/articles/mi_m0EIN/is_2006_June_30/ai_n26913202. The trials were successful and the technology was acquired in March 2008 by Emergent Biosolutions, Inc. Emergent was then awarded a twenty-four million dollar development contract by the Department of Health and Human Services to move the product into clinical trials. *Emergent BioSolutions Receives \$24 Million Development Contract from the Department of Health and Human Services to Fund Continued Development of Anthrax Monoclonal Antibody*, BUS. WIRE, Sept. 3, 2008, available at <http://www.emergentbiosolutions.com/NewsReleases.aspx?ReleaseID=1193342>.

299. Grant descriptions are available through an online searchable database. See Research Portfolio Online Reporting Tools (“RePORT”), NIH, <http://projectreporter.nih.gov/reporter.cfm> (type project name in “term search” box and click “submit query”). A Novel Therapeutic Antibody for Treatment of Ischemic Stroke, available at http://projectreporter.nih.gov/project_info_description.cfm?aid=7480561&icde=5520581; Development of a Novel Method for Inhibiting Atherosclerosis in Diabetes, available at http://projectreporter.nih.gov/project_info_description.cfm?aid=7788206&icde=5520152; Monoclonal Antibodies for Alzheimer’s Immunotherapy, available at http://projectreporter.nih.gov/project_info_description.cfm?aid=7812051&icde=5520848. Another grant, “Monoclonal Antibody Therapy for West Nile Virus” was awarded to Washington University, and NIH indicated that “[t]hese studies are an essential first step in the generation of humanized mAbs that have utility as therapeutic agents against WNV in humans.” Monoclonal Antibody Therapy for West Nile Virus, available at http://projectreporter.nih.gov/project_info_description.cfm?projectnumber=5U01AI061373-03 (emphasis added).

300. 35 U.S.C. § 203(a) (2006).

301. Arno & Davis, *supra* note 297, at A21.

302. 35 U.S.C. § 200.

303. See *supra* Part II.C discussing past treatment of march-in petitions by the NIH. See also Barbara M. McGarey & Annette C. Levey, *Patents, Products, and Public Health: An Analysis of the CellPro March-In Petition*, 14 BERKELEY TECH. L.J. 1095, 1104–06 (1999) (finding that NIH more or less equated “health need” being met with existence of a “safe and effective” product); Senator Birch Bayh, Statement to the National Institutes of Health 4–6 (May 25, 2004) (transcript available at <http://ott.od.nih.gov/policy/meeting/Senator-Birch-Bayh.pdf>) (commenting on intent of Congress in enacting Bayh-Dole Act).

Congress should recognize that the complex biologic market will be bogged down by necessary safety precautions for biosimilars, allowing brand manufacturers to charge exorbitant prices, persisting far beyond the recoup of R&D costs. Congress should further acknowledge the reality that such market conditions will not allow treatments to be reasonably available nor meet public health needs. The legislature needs to adopt a definition of reasonable availability that goes beyond the unduly restrictive applications of the NIH. Specifically, reasonable use of a biologic drug patent should encompass offering that drug for a reasonable price. A reasonable price is not a fixed number and will vary widely depending on R&D costs, demand, and competition.³⁰⁴ For a limited period of time that price will be a monopoly price: one that allows a manufacturer to recoup its R&D costs and make a profit. If a monopoly price persists past that point, however, the price is no longer reasonable.³⁰⁵ Once a profit is being made, charging an exorbitant price is no longer justified if that price severely limits patient accessibility. Allowing corporations to price gouge the medically needy under the guise of business necessity and then defining availability as existing in the market is not acceptable policy.

While the argument for using compulsory licensing to make small-molecule drugs more affordable has not taken hold, monoclonal antibody therapies are distinguishable.³⁰⁶ Small-molecule drugs may be expensive, but Hatch-Waxman ensures a fair market exists.³⁰⁷ The same is not true for antibody drugs because, even with a pathway analogous to Hatch-Waxman, a fair, competitive market is unlikely to develop.³⁰⁸ Additionally, no broad safety problem exists when a generic drug is approved without new clinical trial data. In contrast, complex biologics pose such a safety problem, and encouraging data sharing may help alleviate it.

A generation of astronomically priced antibody drugs will be a significant public health problem. Exorbitant prices negatively affect patients, private health care providers, and government health care programs. The extraordinary circumstances surrounding therapeutic antibody treatments justify the government employing the action of last resort it retains through its financial contribution to the research.³⁰⁹ Pursuant to its duty to protect public health, Congress endowed the government with the power to license intellectual property of an innovating antibody manufacturer for a reasonable royalty and should incentivize successful FOB manufacturers to make complete clinical trial data publically available.

IV. CONCLUSION

Biologics—monoclonal antibodies in particular—pose challenges not faced in the Hatch-Waxman framework. Safety concerns prevent a true “abbreviated” application system from being a realistic goal for antibody drugs. FOB manufacturers will need to

304. Arno & Davis, *supra* note 297, at A21.

305. See H.R. REP. NO. 98-857 pt. II, at 4 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2688 (finding abbreviated approval pathway necessary to mitigate anti-competitive climate of pharmaceutical industry).

306. See *supra* Part I for an overview of the distinguishing factors.

307. See *supra* Part II.B.2 for an explanation of how Hatch-Waxman operates.

308. See *supra* Part III.A for an argument that a competitive market may not develop.

309. See *supra* Part II.C for an explanation of Bayh-Dole march-in rights.

spend millions of dollars on clinical trials in addition to the other high costs associated with bringing a biologic drug to market. Giving the FDA the power to compel licensing and disclosure of the intellectual property associated with an antibody drug will give FOB manufacturers access to key tools and information. They can use those tools to produce drugs as similar as possible to the innovator product, reducing the time and money needed to gain approval. Such a system would allow a competitive monoclonal antibody industry to flourish, ending the perpetual monopolies and ensuring that drugs reach consumers at reasonable prices.

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