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Antitrust and the Biopharmaceutical Industry: Lessons from Hatch-Waxman and an Early Evaluation of the Biologics Price Competition and Innovation Act of 2009

Matthew J. Seamon*

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ANTITRUST AND THE BIOPHARMACEUTICAL INDUSTRY: LESSONS FROM HATCH-WAXMAN AND AN EARLY EVALUATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009*

MATTHEW J. SEAMON**

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* This article is dedicated to the memory of Professor Stephanie Aleong. Although I am honored to have met Professor Aleong, my interactions with her were modest. In choosing this topic, I looked for an issue that Professor Aleong would acknowledge as important. Although this topic is not on the forefront of patients, it does impact their wallets and is subject to exploitation by others and protection from caring and dedicated professionals like Professor Aleong.

** Dr. Seamon is Associate Professor, Pharmacy Practice at Nova Southeastern University College of Pharmacy and serves of Counsel to the firm of Fuerst Ittleman in Miami, Florida where he focuses his practice on Food and Drug Law. Dr. Seamon would like to thank Professor Kathy Cerminara and the Nova Law Review for the opportunity to provide this paper, to Professor Linda Harrison for peeking my interest in antitrust and to Professor Phyllis Coleman for her unwavering support and confidence in me as an attorney. The teacher who "is indeed wise . . . does not bid you [to] enter the house of his wisdom, but rather leads you to the threshold of your own mind." KAHLIL GIBRAN, THE PROPHET 56 (1973). All views expressed in this paper are solely of the author and do not reflect those of Nova Southeastern University or Fuerst Ittleman.

I. INTRODUCTION

In the movie Training Day, veteran police detective Alonzo Harris, played by Denzel Washington, tells rookie police officer Jake Hoyt, played by Ethan Hawke, "This shit's chess not checkers."[1] Although Detective Harris was not talking about the biopharmaceutical industry, he might as well have been. Over the last couple of decades, the U.S. pharmaceutical marketplace has become a sophisticated gaming industry spawned by the Drug Price Competition and Patent Term Restoration Act of 1984, commonly known as Hatch-Waxman.[2] Financial success is predicated on anticipation, responsiveness, business shrewdness, legal adeptness, and industry acumen. Although complicity and collusion may be unlawful, the pharmaceutical industry has pushed the outer boundaries of behavior for profit and penetration. Consider the incentive—the average cost to develop a new biotechnology product is $1.2 billion and only one-third of drugs approved recoup research and development costs.[3] The risk is high. However, the upside is substantial. Blockbuster drugs generate billions in sales annually with certain drugs earning in excess of ten billion dollars annually.[4]

1. TRAINING DAY (Warner Bros. 2001).

2. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2006)).

3. *Average Cost to Develop a New Biotechnology Product Is $1.2 Billion*, MED. NEWS TODAY, Nov. 11, 2006, http://www.medicalnewstoday.com/printerfriendlynews.php?newsid=56377.

4. Stephanie Saul, *For Jarvik Heart Pioneer, Drug Ads Raise Profile and Questions*, N.Y. TIMES, Feb. 7, 2008, at A1 (Lipitor, marketed by Pfizer, reportedly achieved sales of $12.7 billion in 2007).

Biologics represent the evolving future of prescription drug therapy.[5] They have already revolutionized the treatment of cancer, diabetes, hemophilia, and rheumatoid arthritis, among other diseases. As the human genome is mapped to completion, research and development is now identifying important genetic predispositions and novel targets for therapy that will further restructure medicine. We are truly at the threshold of a paradigm shift in drug therapy. Herceptin, a monoclonal antibody drug used to treat a deadly form of breast cancer, has been shown to reduce the risk of death by 33%.[6] Nevertheless, the costs of biologics are immense.[7] A single biologic can cost upwards of $200,000 annually.[8] In 2007 Americans spent over forty billion dollars for biological drugs and they now account for approximately 20% of global drug sales.[9] It is estimated that 50% of the pharmaceutical market is represented by biologics.[10]

To confound the situation, there is a newly legislated, but not yet implemented approval pathway for generic biologics in the United States authorized under the Biologics Price Competition and Innovation Act of 2009 (BPCIA).[11] Prior to this act, for a generic biologic to become available, the sponsor had to conduct lengthy and costly research; essentially the same requirements as an innovator drug.[12] Thus, the research and development costs remained significant and the cost to the patient would be only marginally decreased. Additionally, as approval would only be considered a follow-up without significant cost-savings, many would be reluctant to "switch," and sponsors were disinclined to develop these products.[13] Accordingly, brand biologics had a functional patent life in perpetuity and the incentive to compete was trivial. For example, recombinant human insulin by Lilly was ap-

5. Alfred B. Engelberg et al., *Balancing Innovation, Access, and Profits—Market Exclusivity for Biologics*, 361 NEW ENG. J. MED. 1917, 1917 (2009).

6. Edward H. Romond et al., *Trastuzumab Plus Adjuvant Chemotherapy for Operable HER2-Positive Breast Cancer*, 353 NEW ENG. J. MED. 1673, 1673 (2005).

7. Engelberg et al., *supra* note 5, at 1917.

8. *Id.*

9. Doug Trapp, *Biologics Don't Need Long Market Exclusivity, FTC Says*, AMEDNEWS.COM, June 29, 2009, http://www.ama-assn.org/amednews/2009/06/29/gvsc0629.htm; NILS BEHNKE ET AL., BAIN & CO., BIOSIMILARS: A MARATHON, NOT A SPRINT 1 (2009), *available at* http://www.bain.com/bainweb/PDFs/cms/Public/2009_BB_Biosimilars.pdf.

10. Linda Hull Felcone, *The Long and Winding Road to Biologic Follow-Ons*, BIOTECHNOLOGY HEALTHCARE, May 2004, at 20.

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

12. Engleberg et al., *supra* note 5, at 1918.

13. *See id.*

proved in 1982, and there remains no generic for this billion dollar drug.[14] However, on March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act, a health reform bill, which, in part provided statutory authority for biosimilar products, like Hatch-Waxman established for traditional drugs.[15]

Although Hatch-Waxman is often viewed as a wide success, it has a number of important flaws that should serve instructional in the evaluation of the new regulatory framework for generic biologics.[16] Additionally, Europe has a pathway in place to provide further insight and experience, and a Canadian system is approaching final implementation.[17] There are important lessons to be learned and a properly structured approval pathway for generic biologics will prove to be advantageous.

Part II of this paper presents antitrust concerns in the current biopharmaceutical marketplace. It looks at the current system of patents and exclusivity and evaluates the economic framework that makes biopharmaceuticals so unique and susceptible to peculiar business practices. Part III of this paper presents the Food and Drug Administration's (FDA) regulatory role in prescription drug regulation and then underscores the current business practices of the biopharmaceutical industry. It establishes that the future of medicine is biologically based and the need for a properly structured pathway for generic biologics. Part IV of this paper reviews the regulatory framework involving prescription drugs, including biologics. Part V deconstructs the Hatch-Waxman provisions to the Food, Drug, and Cosmetic Act of 1983 (FDCA) and surmises limitations to the amendment, serving as foundation for the evaluation of the BPCIA. Part VI of the paper reviews the current state of generic biologics and evaluates the new legislation in the U.S. using the E.U. legislation as a benchmark. Part VII assesses the future of follow-

14. DEPT. OF HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (30th ed. 2010), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf [hereinafter DEP'T OF HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS] (listing all drugs approved since 1984 exclusive biologics licensed under the PHSA, and commonly referred to as the Orange Book based on the color); *see also* Press Release, Eli Lilly & Co., Lilly Reports Fourth-Quarter and Full-Year 2009 Results (Jan. 28, 2010), *available at* http://files.shareholder.com/downloads/LLY/885688091x0x347040/8c632725-1694-4968-bb85-8f0c14a8ca95/LLY_News_2010_1_28_Financial.pdf.

15. *Id.*

16. *See* 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, 188, 198, 200 (2008).

17. *See* Behnke et al., *supra* note 9, at 2.

up biologics in the U.S. in light of the evolving framework and provides concluding remarks on the topic.

II. REGULATORY AND ECONOMIC OVERVIEW

In order to appreciate the gamesmanship involving biologics and drugs one must need to understand the regulatory interplay between antitrust law and patents and the economic framework surrounding prescription drugs.

A. *Antitrust Considerations*

Antitrust involves the balance between government granted monopoly in the form of patents and other intellectual property rights, and the abuse of monopoly power to hinder competition.[18] It serves to protect the integrity of the competitive process and enable consumers wide access to the best possible products at the lowest possible prices. It serves to try and level the playing field for all players in a market.

Antitrust legislation originated in the late 1800s while certain businesses, called trusts, controlled entire industries, most notably steel and oil.[19] As expected, prices soared while quality and services diminished.[20] In response to growing concern, President Theodore Roosevelt and Congress led the bust of these trusts, through pioneering antitrust legislation.[21] Antitrust legislation has shown to lower prices, improve service and spawn vigorous competition.[22] Amazingly, it is some of the most direct and succinct law on the books. It is elegant in its simplicity. Consider Section 1 of the Sherman Act is ninety-six words and outlaws "[e]very contract, combination . . . or conspiracy in restraint of trade."[23] Section 2 is eighty-two words and finds "[e]very person who shall monopolize, or attempt to monopolize . . . guilty of a felony."[24] The impact of these 178 words has evolved an encyclopedia

18. *See* FTC Fact Sheet: Antitrust Laws: A Brief History, 1, http://www.ftc.gov/bcp/edu/microsites/youarehere/pages/pdf/FTC-Competition_Antitrust-Laws.pdf [hereinafter FTC Fact Sheet].

19. *Id.* John D. Rockefeller, founder of Standard Oil Company, reportedly amassed a net worth of over a billion dollars making him the world's first billionaire. John D. Rockefeller, http://www.johndrockefeller.org (last visited Apr. 17, 2010).

20. FTC Fact Sheet, *supra* note 18, at 1; *see also* Rudolph J.R. Peritz, *The Sherman Anti-Trust Act of 1890*, *in* HISTORIANS ON AMERICA, DECISIONS THAT MAKE A DIFFERENCE 31, 33 (2007), *available at* http://www.america.gov/media/pdf/books/historians-on-america.pdf#pop up.

21. Peritz, *supra* note 20, at 35.

22. *Id.* at 35–36.

23. 15 U.S.C. § 1 (2006).

24. 15 U.S.C. § 2.

of case law, has allowed U.S. businesses to develop new industries, and has provided U.S. consumers remarkable services and products at reasonable prices. Today, antitrust legislation remains a vital aspect to competition and affects such diverse industries as cable television, telephone service, internet search engines, and computer operating systems.

Antitrust legislation encompasses federal antitrust laws, enforced by the Department of Justice and state antitrust laws, enforced by state attorneys general.[25] Antitrust cases involving drugs are primarily within the purview of the FTC Bureau of Competition, Health Care Services, and Products Division, which generally regulates the pharmaceutical industry.[26] Antitrust legislation provides for suits by the injured party[27] including State Attorneys General,[28] and the award of injunctive relief.[29] Antitrust law involving drugs is based primarily in Section 1 of the Sherman Act—trusts;[30] Section 2 of the Sherman Act—monopolies;[31] Section 2 of the Clayton Act, commonly referred to as the Robinson-Patman Act—prohibiting price discrimination;[32] Section 3 of the Clayton Act—dealing with exclusionary practices, such as tying arrangements and predatory pricing;[33] Section 7 of the Clayton Act—affecting mergers and acquisitions;[34] Hart-Scott-Rodino—involving premerger notification;[35] and Section 5 of the FTC Act—preventing unfair and deceptive business practices.[36]

B. *Patents and Exclusivity*

Patent law involves "the right to exclude others from making, using, offering for sale, or selling [an] invention throughout the United States or importing [an] invention into the United States."[37] Patents are granted to products based on utility, novelty,[38] and non-obviousness.[39] Patent law is consti-

25. *See* FED. TRADE COMM'N, OVERVIEW OF FTC ANTITRUST ACTIONS IN PHARMACEUTICAL SERVICES AND PRODUCTS 1, 6, 8 (2008), *available at* http://www.ftc.gov/bc/0608rxupdate.pdf [hereinafter FTC 2008 REPORT].

26. *Id.* at 1.

27. 15 U.S.C. § 15(a) (2006).

28. 15 U.S.C. § 15(c).

29. 15 U.S.C. § 26.

30. 15 U.S.C. § 1.

31. 15 U.S.C. § 2.

32. 15 U.S.C. § 13 (commonly referred to as the Anti-Chain Store Act).

33. 15 U.S.C. § 14.

34. 15 U.S.C. § 18.

35. 15 U.S.C. § 18(a).

36. 15 U.S.C. § 45.

37. 35 U.S.C. § 154(a)(1) (2006).

38. 35 U.S.C. § 102.

tutionally based and within the federal purview.[40] Article 1, Section 8 of the U.S. Constitution reads "Congress shall have Power . . . [t]o 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."[41] Patent law serves to foster innovation by protecting the interest of the innovator and to prevent copycats that simply pilfer the reward.[42] The United States Patent and Trademark Office (USPTO) is the federal agency responsible for granting patents and is an Agency in the U.S. Department of Commerce.[43]

There are three types of patents available for prosecution.[44] Drug patents primarily incorporate utility patents and typically involve the drug product, formulation, manufacturing process, and method of use.[45] Theoretically, all patented drugs are subject to replication, including complex biologicals.[46] A properly filed patent, must

> contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.[47]

When talking about drugs and biologics another important aspect to consider is exclusivity.[48] Exclusivity refers to "exclusive marketing rights granted by the FDA upon approval of a drug."[49] Patents are granted by the U.S. Patent and Trademark Office based on statutory requirements, whereby

39. 35 U.S.C. § 103.

40. *See* U.S. CONST. art. 1, § 8; 35 U.S.C. § 1.

41. U.S. CONST. art. 1, § 8.

42. *See* U.S. Patent and Trademark Office, Who We Are, http://www.uspto.gov/about/index.jsp (last visited Apr. 17, 2010).

43. 35 U.S.C. § 1.

44. U.S. Patent and Trademark Office, Patent Process, http://www.uspto.gov/patents/process/index.jsp#heading-2 (last visited Apr. 17, 2010). Design patents are issued for ornamental designs; plant patents are issued for distinct and new varieties of plants; utility patents are issued for any "process, machine, article of manufacture, [or] composition of matter," or any new and useful improvement thereof. *Id.*

45. Terry G. Mahn, *Patenting Drug Products: Anticipating Hatch-Waxman Issues During the Claims Drafting Process*, 54 FOOD & DRUG L.J. 245, 246 (1999).

46. *See* Pathway for Biosimilars Act, H.R. 5629, § 101(a)(2) 110th Cong. (2008).

47. 35 U.S.C. § 112 (2006).

48. *See* FDA, Frequently Asked Questions on Patents and Exclusivity, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079031.htm (last visited Apr. 17, 2010).

49. *Id.*

exclusivity is granted by the FDA upon a drug's proof of safety and efficacy.[50] Patents are granted for twenty years.[51] Exclusivity depends on the type of patent issued and is typically five years.[52] Although an innovator drug may have no patent protection remaining, once it is approved by the FDA it gains a period of exclusivity, whereby the FDA cannot approve a generic competitor.[53]

The interplay between patent law and antitrust law strikes an important and delicate balance between competing interests.[54] Patents are government granted monopolies, while antitrust is government's bust of monopolies.[55] The two are in complete philosophical opposition.[56] Interestingly, however, both seek to accomplish the same end: increase innovation.[57] Patents seek this by directly rewarding innovation and making public information on existing products to help promote further research and development, thus paying it forward.[58] Antitrust seeks to promote innovation through a leveling of the competitive process, thus allowing new innovators to research and reward.[59]

Trade secrets are another intellectual property right, like patents, but with critical differences.[60] Trade secrets refer to "any information that can be used in the operation of a business or other enterprise and that is sufficiently valuable and secret to afford an actual or potential economic advantage over others."[61]

> A trade secret may consist of any formula, pattern, device or compilation of information which is used in one's business, and which gives him an opportunity to obtain an advantage over competitors who do not know or use it. It may be a formula for a chemical compound, a process of manufacturing, treating or preserving ma-

50. *See* 35 U.S.C. § 1; 21 C.F.R. § 314.108 (2009).
51. 35 U.S.C. § 154(a)(2).
52. 21 C.F.R. § 314.108(b)(2).
53. *See id.*
54. *See* Christopher R. Leslie, *Antitrust and Patent Law as Component Parts of Innovation Policy*, 34 J. CORP. L. 1259, 1260 (2009).
55. *Id.* at 1259.
56. *See id.*
57. *Id.* at 1260.
58. *See id.* at 1261.
59. *See* Leslie, *supra* note 54, at 1263–64.
60. *See* RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 39 cmt. c (1995).
61. RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 39.

> terials, a pattern for a machine or other device, or a list of customers.[62]

Generally speaking, to be protected, a trade secret must be kept secretive, be of value, and provide a competitive business advantage.[63] Trade secrets differ from patents in three important regards.[64] First, a trade secret can survive indefinitely, unlike a patent which expires after twenty years.[65] Secondly, a trade secret does not involve disclosure of any information and in fact requires the holder to conceal the practice.[66] Thirdly, trade secrets offer no real protection against reverse engineering and copy.[67] The classic example of a trade secret is the recipe for Coca-Cola. If Coca-Cola sought patent protection, they would have to disclose the recipe and then receive protection for only the statutory time.[68] Not a great business practice for the Atlanta based company using a recipe from Pharmacist John Pemberton, developed over one hundred years ago.[69] However, if at any point a competitor can legally determine the recipe, Coca-Cola is at a complete loss for compensation or harm.[70]

The pharmaceutical marketplace does not typically rely on trade secrets to protect innovation.[71] Although the protection afforded is expansive, the risk is too great.[72] Pharmaceutical companies notoriously employ a number of competitive intelligence systems, and the technology used to reverse engineer drugs is rather simple for those in the business.[73] Instead, the major pharmaceutical companies rely on patent protection and urbane marketing

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62. RESTATEMENT (FIRST) OF TORTS § 757 cmt. b (1939).

63. FLA. STAT. § 812.081(1)(c) (2009).

64. *See* RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 39 cmt. c.

65. *See id.*; 35 U.S.C. § 154(a)(2) (2006).

66. *See* RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 39 cmt. c, f.

67. *See* RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 39 cmt. c.

68. *See* 35 U.S.C. § 112; 35 U.S.C. § 154(a)(2).

69. John Stith Pemberton: Who Invented Coca-Cola?, The Chronicles of Coca-Cola, http://www.thecoca-colacompany.com/heritage/chronicle_birth_refreshing_idea.html (last visited Apr. 17, 2010).

70. *See* RESTATEMENT (THIRD) OF UNFAIR COMPETITION § 39 cmt. b; 18 U.S.C. § 1832 (2006) (misappropriation of a trade secret for economic harm is unlawful).

71. *See* PHARM. RESEARCH & MFRS. OF AM., DELIVERING ON THE PROMISE OF PHARMACEUTICAL INNOVATION: THE NEED TO MAINTAIN STRONG AND PREDICTABLE INTELLECTUAL PROPERTY RIGHTS 7 (2002) [hereinafter PHRMA, DELIVERING ON THE PROMISE].

72. *See id.*

73. *See* Phoebe M. Roberts & William S. Hayes, *Information Needs and the Role of Text Mining in Drug Development*, 13 PAC. SYMP. ON BIOCOMPUTING 592, 596 (2008), *available at* http://psb.stanford.edu/psb-online/proceedings/psb08/roberts.pdf.

campaigns to maximize profits, as accountability to shareholders is an important obligation.[74]

C. *Economic Framework*

The pharmaceutical industry has a very unique economic framework based on the styles of competition, manufacturing issues, research and development costs, barriers to entry, and elasticity of demand.

Life saving therapies, and drugs in general, are said to have inelastic demand.[75] Practically speaking this means as the price increases, the demand stays the same regardless of supply. In classic economic theory, a product's price is viewed as the equilibrium point between supply and demand in a perfectly competitive marketplace.[76] However, in a situation like Type I diabetes where you need insulin to survive, the relationship between supply and demand is irrelevant to establish a price point. A diabetic will pay whatever price possible, independent of the supply.

Another important economic consideration involving drugs is pricing.[77] There is no price regulation in the United States, although every other Westernized country has some regulation.[78] For example, there are direct price regulations in Canada, France and Italy.[79] Indirect regulations exist in Japan —insurance reimbursements—and the United Kingdom—profits.[80] Pricing is extremely complex in the United States as insurance, managed care, and government payers confound the situation, and the inelasticity of demand supports high pricing.[81] Drugs are further unique in that they involve important economies of scale.[82] An established pharmaceutical manufacturing

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74. *See id.* at 592–93.

75. *See* Economics A–Z: Elasticity, The Economist, http://www.economist.com/research/economics/alphabetic.cfm?letter=E (last visited Apr. 17, 2010).

76. *See* Supply and Demand, Dictionary.com, http://dictionary.reference.com/browse/supply and demand (last visited Apr. 17, 2010). Alfred Marshall was a British economist who is credited with identifying supply and demand in his text, *Principles of Economics*, published in 1890. *See generally* ALFRED MARSHALL, PRINCIPLES OF ECONOMICS (Prometheus Books 1997) (8th ed. 1920).

77. *See* Neeraj Sood et al., *The Effect of Regulation on Pharmaceutical Revenues: Experience in Nineteen Countries*, 28 HEALTH AFF. (Web Exclusive) w125, w125 (2008).

78. *See id.* at w136.

79. *See id.* at w127.

80. *See id.* at w130–31.

81. *See, e.g.*, Allison K. Young & Meredyth Smith Andrus, *Pharmaceutical Pricing and Hatch-Waxman Reform: The Right Prescription*, 1 J. GENERIC MEDS. 228, 229 (2004).

82. *See* Patricia M. Danzon, *Economics of the Pharmaceutical Industry*, NAT'L BUREAU OF ECON. RESEARCH, Research Summary 2006, www.nber.org/reporter/fall06/danzon.html (last visited Apr. 17, 2010).

facility can manufacturer drugs at a nominal cost. This does not hold *as true* for biologics, which may have a considerable cost associated with manufacture, but economies of scale still ring true as with all large scale productions and industries.[83] Once the facility is established, the cost to produce is rather low.

The pharmaceutical industry is inimitable in that it encompasses three types of competition, each with unique economic considerations.[84] First, there is brand/brand competition.[85] This typically involves drugs in the same class and drugs used for similar indications.[86] An example of this is Viagra and Cialis. The second type of competition is brand/generic.[87] This occurs when a drug loses its exclusivity and patent protection and a generic drug becomes available.[88] An example of this is Prozac and fluoxetine, manufactured by a generic company. The third type of competition among drugs is generic/generic..[89] As drugs lose their patents, generics become available.[90] An example of this might include fluoxteine—by Mylan Pharmaceuticals—and fluoxetine—by Teva Pharmaceuticals.

Barriers to entry are another essential concept in understanding the interplay between patent and antitrust with drugs. Drug development is considered to have a slow speed of entry and new players are at a considerable disadvantage.[91] It takes approximately eight years to develop a drug from initial research to market approval.[92] And this is for skilled players. A new company seeking to research and develop a drug would face a number of challenges, including necessary supplier agreements, specialized industry regulation and intellectual property right considerations, sunken costs, and susceptibility to predatory pricing.

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83. *See id.*

84. *See* CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS HAS AFFECTED PRICES AND RETURNS IN THE PHARMACEUTICAL INDUSTRY xi (1998), *available at* http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf [hereinafter CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS].

85. *See id.*

86. *See id.*

87. *See id.* at xii–xiii.

88. *See id.*

89. *See* CONG. BUDGET OFFICE, HOW INCREASED COMPETITION FROM GENERIC DRUGS, *supra* note 84, at xiii.

90. *See id.*

91. *See* Red Orbit News, New Drugs Are Taking Longer to Bring to Market in the U.S., According to Tufts Center for the Study of Drug Development, http://www.redorbit.com/news/health/291272/new_drugs_are_taking_longer_to_bring_to_market_in/ (last visited Apr. 17, 2010).

92. *See Average Cost to Develop a New Biotechnology Product Is $1.2 Billion*, *supra* note 3.

As a result of these factors, the pharmaceutical marketplace has evolved into a true oligopoly. As such, there is a great incentive for price fixing, conscious parallelism, tacit collusion and collusive pricing tendencies, along with heavy reliance on game theory.[93] Not surprisingly, the industry has faced accusations of monopolization, agreements not to compete, agreements on price or price-related terms, predatory pricing, unlawful horizontal mergers between competitors, vertical mergers involving PBMs, potential competition mergers, illegal tying, and other arrangements.[94]

III. INDUSTRY OVERVIEW AND REGULATION

The pharmaceutical industry is a competitive and potentially very lucrative marketplace. Profits are measured in billions of dollars in annual sales and unexpected, sudden market collapses are not uncommon. One day Vioxx was a jackpot with sales of $2.5 billion annually; the next it was a liability estimated at $50 billion to Merck.[95] Black-box warnings, other labeling revisions, and competing drug approvals incessantly threaten a drugs survival and profitability.[96] One in five drugs will see a black-box warning or require market withdrawal in a twenty-five year life-span.[97] Loss of patents protection is another critical issue. Within two months of losing patent protection, Prozac lost 70% of its multibillion dollar market share.[98]

A. *FDA Oversight*

The FDA is one of eleven agencies of the Health and Human Services (HHS) which is the department responsible for "protecting the health of all Americans."[99] The statutory functions of the FDA are formally delegated to

93. *See* Julia Rosenthal, *Hatch-Waxman Use or Abuse? Collusive Settlements Between Brand-Name and Generic Drug Manufacturers*, 17 BERKELEY TECH. L.J. 317, 319–20 (2002).

94. *See* FTC 2008 REPORT, *supra* note 25.

95. *See* Aaron Smith, *Jury: Merck Negligent*, CNNMONEY.COM, Aug. 22, 2005, http://money.cnn.com/2005/08/19/news/fortune500/vioxx/index.htm; Matthew Herper, Merck Vioxx Liability Could Near $50 Billion, FORBES.COM, Aug. 22, 2005, http://www.forbes.com/2005/08/22/merck-vioxx-liability-0822markets01.html.

96. *See* Karen E. Lasser et al., *Timing of New Black Box Warnings and Withdrawals for Prescription Medications*, 287 JAMA 2215 (2002).

97. *Id.* at 2216.

98. Richard G. Frank, *Regulation of Follow-on Biologics*, 357 NEW ENG. J. MED. 841, 842 (2007).

99. Department of Health & Human Services, About HHS, http://www.hhs.gov/about/ (last visited Apr. 17, 2010).

the Secretary of the HHS,[100] who is appointed by the President and is a member of the President's cabinet.[101] The FDA ensures safe and effective drugs to U.S. consumers, in addition to a myriad of other roles.[102] The FDA also oversees food, veterinary medicines, dietary supplements, medical devices, radiation emitting devices, and cosmetics.[103] The FDA has six product centers, one research center, and two offices within the agency that regulate its various responsibilities.[104] The Center for Drug Evaluation and Research (CDER) is the largest center in the FDA and is charged with prescription and non-prescription drugs.[105] The Center for Biologics Evaluation and Research (CBER) is responsible for biologics including some drugs. [106]

Like all administrative agencies, the FDA has three essential functions: rulemaking authority, investigative/enforcement authority, and adjudicatory

100. FDA, FDA Staff Manual Guides, Volume II, Delegations of Authority: Regulatory Delegations of Authority to the Commissioner Food and Drugs, http://www.fda.gov/AboutFDA/ReportsManualsForms/StaffManualGuides/ucm080711.htm (last visited Apr. 17, 2010).

101. *See* MCDERMOTT, NEWS, (McDermott Will & Emery), President Obama Announces FDA Commissioner and Deputy Commissioner Appointments (Mar. 16, 2009), http://www.mwe.com/index.cfm/fuseaction/publications.nldetail/object_id/d878770f-69b9-455f-a879-250d5caf9c6d.cfm. The Current FDA Commissioner is Dr. Margaret Hamburg. FDA, Commissioner's Page, http://www.fda.gov/AboutFDA/CommissionersPage/default.htm (last visited Apr. 17, 2010). The Current HHS Secretary is Kathleen Sebelius. Dep't of Health & Human Servs., Kathleen Sebelius Confirmed as Secretary of the Department of Health and Human Services, http://www.hhs.gov/secretary/ (last visited Apr. 17, 2010).

102. FDA, What the Food and Drug Administration Regulates, http://fda.org/index.php?article=what-the-food-and-drug-administration-regulates (last visited Apr. 17, 2010). Administrative agencies are a product of the legislation to oversee complex matters of Government. The FDA implements the rules and regulations while Congress paints with broad brush strokes on food and drug issues.

103. *Id.*

104. FDA, Organization Chart, http://www.fda.gov/downloads/AboutFDA/CentersOffices/OrganizationCharts/UCM198460.pdf. The newest center in the FDA is the Center for Tobacco Products established upon passage of Family Smoking Prevention and Tobacco Control Act on June 22, 2009. News Release, FDA, FDA Launches New Center for Tobacco Products, (Aug. 19, 2009), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm179410.htm (last visited Apr. 17, 2010); Family Smoking Prevention and Tobacco Control Act, Pub. L. No. § 111–31, 123 Stat. 1776, 1776 (2009). This act gave the FDA new authorities over tobacco including a ban on certain flavored cigarettes, requiring companies to fully disclose ingredients and additives, prohibiting the terms "light" and "mild," and stopping youth-focused marketing. *See id.* at 1784, 1799, 1831.

105. FDA, How Drugs Are Developed and Approved, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/default.htm (last visited Apr. 17, 2010).

106. FDA, About the Center for Biologics Evaluation and Research, http://www.fda.gov/AboutFDA/CentersOffices/CBER/default.htm (last visited Apr. 17, 2010).

power.[107] Nevertheless, administrative agencies are often referred to as a headless, fourth branch of government as their rulemaking authority is granted by the legislature, their investigative and enforcement authority is accountable to the Executive branch, and their adjudicatory authority is subordinate to the court system. These inherent limitations have often inhibited the FDA and account for many of the claims made by its detractors.

The FDA regulates approximately $1 trillion worth of goods,[108] with an annual budget of $3.2 billion.[109] Approximately $828 million of this budget originates from user fees.[110] These user fees were first established in 1992 in response to growing concern about the efficiency of the FDA's review process when Congress enacted the Prescription Drug User Fee Act (PDUFA I).[111] PDUFA reauthorizes every five years.[112] PDUFA affords the FDA the opportunity to hire reviewers and expedites the drug approval process.[113] The most recent enactment, PDUFA IV, was included in Title I of the Food and Drug Administration Amendments Act of 2007 (FDAAA).[114] Under PDUFA, the FDA collects three types of user fees from the industry: application fees, establishment fees, and product fees.[115] PDUFA has been heavily criticized as the regulators—the FDA—have now become very tight bedfellows with the industry, and the agency now relies on this funding for sur-

107. *See* JOHN P. SWANN, FDA'S ORIGIN, http://www.fda.gov/AboutFDA/WhatWeDo/History/Origin/ucm124403.htm (adapted from A HISTORICAL GUIDE TO THE U.S. GOVERNMENT (George Kurian, ed. 1998)).

108. FDA, FAQs by Topic, http://www.fda.gov/AboutFDA/WhatWeDo/FAQs/default.htm (last visited Apr. 17, 2010).

109. FDA, Summary of the FDA's FY 2010 Budget, http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/BudgetReports/ucm153154.htm (last visited Apr. 17, 2010). The budget for 2010 specifically includes a section on generic biologics—referred to as "Follow-on Biologics." *Id.*

110. *Id.*

111. *See* 21 U.S.C. § 379g–h (2006).

112. *See* FDA, White Paper Prescription Drug User Fee Act (PDUFA): Adding Resources and Improving Performance in FDA Review of New Drug Applications, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm119253.htm (last visited Apr. 17, 2010) [hereinafter FDA, White Paper].

113. *Id.*

114. *See* FDA, PDUFA Legislation and Background: PDUFA IV, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm144411.htm (last visited Apr. 17, 2010).

115. FDA, White Paper, *supra* note 112; *see also* FDA, Small Business Assistance: Frequently Asked Questions on Prescription Drug User Fees (PDUFA), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069943.htm (last visited Apr. 17, 2010); Prescription Drug User Fee Rates for Fiscal Year 2010, 74 Fed. Reg. 38,451, 38,451 (Aug. 3, 2009).

vival, a very alarming proposition.[116] User fees account for approximately fifty percent of drug review costs.[117]

In determining which products are assessed user fees, the FDA widely utilizes a reference entitled *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*.[118] This reference includes all drug products approved by the FDA since 1984 including therapeutic equivalents, so called generic drugs.[119] Drugs listed in the *Orange Book* are assumed to be marketed and thus qualify for user fees.[120] The *Orange Book* also serves as the official compilation of patent and exclusivity listings of drugs recognized by the FDA.[121]

B. *Research and Development*

The drug approval process is a costly, complex, and cumbersome one. In the screening and development phase, a myriad of laboratory compounds are thoroughly screened for activity.[122] So called "hits" are then further tested for "leads" in a process coined hits-to-leads.[123] Medicinal chemists work to identify and then (re)engineer the most active and stable compounds to focus further development, all in the hopes of finding the next blockbuster.[124] Compounds, most active *in vitro*, are administered to rodents and then primates to assess plausibility in humans.[125] Products appearing promising can then be administered to humans in a complex and closely monitored system of escalating doses and monitoring.[126] Products are further tested for carcinogenicity, mutagenecity, and teratogenecity.[127]

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116. *See* FDA, White Paper, *supra* note 112.

117. *Id.*

118. Natalie M. Derzko, *The Impact of Recent Reforms of the Hatch-Waxman Scheme on Orange Book Strategic Behavior and Pharmaceutical Innovation*, 45 IDEA 165, 169 (2005).

119. *See id.* at 167, 169.

120. *See* DEP'T OF HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS, *supra* note 14, at ix.

121. *Id.* at i.

122. FDA, Investigational New Drug (IND) Application, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm (last visited Apr. 17, 2010) [hereinafter FDA, IND].

123. Konrad H. Bleicher et al., *Hit and Lead Generation: Beyond High-Throughput Screening*, 2 NATURE REV. DRUG DISCOVERY 369, 371 (2003).

124. *Id.* at 377.

125. *See* 21 C.F.R. § 314.50(d)(2) (2009).

126. *See* 21 C.F.R. § 312.21.

127. *See* 21 C.F.R. § 312.32(c)(B).

Before administering a so called investigational drug to humans, the sponsor must seek an Investigational New Drug Application (IND).[128] Technically, this serves as legal permission to move an unapproved, investigational drug into the stream of interstate commerce.[129] The application has three focus areas: 1) animal pharmacology and toxicology; 2) chemistry and manufacturing; and 3) clinical protocols and investigator information.[130] The FDA reviews this application with an eye on safety and future development, all the while understanding that drug development is inherently dangerous, but necessary.[131] The FDA has a thirty day window to issue a "clinical hold" on an IND, or else the application is deemed approved and the drug can then be administered to human subjects in the first of a series of research protocols.[132]

Phase I studies are the first studies involving humans.[133] The drug is typically administered to a small number of healthy male volunteers, usually between ages twenty and eighty.[134] The drug is evaluated for the preferred route of administration, a tolerable dosage range, safety and side effects, and reviewed for its pharmacokinetic characteristics.[135] Next, Phase II studies are conducted whereby the drug is administered to a population of interest, usually about 200 patients inflicted with the disease, but otherwise healthy.[136] These studies establish preliminary efficacy data, identify the preferred dosing regimen and target dose, and further assess safety.[137] Phase III studies are typically large scale randomized, controlled and uncontrolled trials involving thousands of patients to substantiate efficacy, expand safety data, and confirm the optimal dose.[138]

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128. *See* 21 U.S.C. § 355(j) (2006); *see also* 21 C.F.R. § 312. IND is also referred to as "Notice of Claimed Investigational Exemption for a New Drug." 21 C.F.R. § 312.3(b).

129. *See* 21 U.S.C. § 355(a); 21 C.F.R. § 312.

130. FDA, IND, *supra* note 122.

131. *See id.*

132. CTR. FOR DRUG EVALUATION & RESEARCH, U.S. FOOD & DRUG ADMIN, MANUAL OF POLICIES AND PROCEDURES 6030.1 2 (1998), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM082022.pdf [hereinafter CDER, 1998 POLICIES AND PROCEDURES].

133. 21 C.F.R. § 312.21(a)(1).

134. *Id.*; *see also* FDA, Inside Clinical Trials: Testing Medical Products in People, http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143531.htm (last visited Apr. 17, 2010).

135. 21 C.F.R. § 312.21(a). Pharmacokinetic characteristics refer to the body's action on a drug. *See* 21 C.F.R. § 312.23(a)(5). That is, absorption, distribution, metabolism, and elimination/excretion. 21 C.F.R. § 312.23(a)(8)(i).

136. 21 C.F.R. § 312.21(b).

137. *See id.*

138. 21 C.F.R. § 312.21(c).

Overall, the research and development process is a risky endeavor. The top ten pharmaceutical companies bring an average of only 0.6 drugs to market per year.[139] Only five out of five thousand compounds make it to human testing, of which only one is ultimately approved for human use.[140] Then remarkably, only one-third of drugs approved generate sufficient earnings to recoup average research and development costs.[141]

C. *Marketing Strategies Employed*

In response to the highly risky, yet lucrative business of pharmaceuticals, the industry has developed a complex multi-faceted approach to increasing sales, promoting widespread, and some would say indiscriminate use, and discerning themselves from the competition.[142] Drug companies hire celebrity spokespersons and cheerleaders as sale associates.[143] They utilize a sophisticated system of data mining to identify changes in market share and physician identifiable prescribing habits.[144] The industry has even been accused of creating diseases and selling sickness.[145] They have an infamous reputation for providing lavish incentives to physicians for the mere opportunity to detail them on the benefits of their product.[146] They regularly masquerade marketing as "educational symposia and seminars."[147] Companies seed the market through the use of "free" drug samples and low cost in-hospital contracts.[148] They use prominent physician names, along with ghost writers in medical publications and have even gone so far as to establish journals.[149] Although these tactics may be facially legal, the ethical consid-

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139. *Big Pharma-Biotech Partnering Holds Promise for Improving R&D Productivity*, MED. NEWS TODAY, Mar. 26, 2007, http://www.medicalnewstoday.com/articles/66151.php.

140. Tufts Ctr. for the Study of Drug Dev., *Backgrounder: How New Drugs Move Through the Development and Approval Process* (2001), *available at* http://csdd.tufts.edu/files/uploads/how_new_drugs_move.pdf.

141. *Ten Percent of New Prescription Drugs Generate Half of the Industry's Net Returns*, BUSINESS WIRE (New York), Dec. 13, 2002, at 1.

142. *See* RAY MOYNIHAN & ALAN CASSELS, SELLING SICKNESS: HOW THE WORLD'S BIGGEST PHARMACEUTICAL COMPANIES ARE TURNING US ALL INTO PATIENTS x–xviii (2005).

143. *Id.* at 41; Stephanie Saul, *Gimme an Rx! Cheerleaders Pep Up Drug Sales*, N.Y. TIMES, Nov. 28, 2005, at A1.

144. *See* Michael Heesters, Comment, *An Assault on the Business of Pharmaceutical Data Mining*, 11 U. PA. J. BUS. L. 789, 789 (2009).

145. *See* MOYNIHAN & CASSELS, *supra* note 142, at xi–xii.

146. *Id.* at 23.

147. *See id.* at 26.

148. *See id.* at 23–24.

149. *Id.* at 25; Posting of Bob Grant, Merck Published Fake Journal, to http://www.the-scientist.com/blog/display/55671 (Apr. 30, 2009); *see also* Joseph S. Ross et al., *Guest Au-*

erations are notable. Direct-to-consumer advertising (DTCA) of drugs has become a great windfall for the industry since 1997 when the FDA issued a draft guidance that effectively enabled the use of broadcast ads for DTCA.[150] Currently, only the United States and New Zealand allow DTCA of pharmaceutical products.[151]

In addition to FDA regulation, the industry highly self-regulates. PhRMA, the pharmaceutical trade association, publishes a Code on Interactions with Healthcare Professionals, which provides ethical guidance on industry practice.[152] The updated code took effect in January 2009 and includes a number of changes targeting some of the above mentioned practices.[153] The other major regulatory guidance is published by the Office of the Inspector General of the Department of Health and Human Services and is called the Compliance Program Guidance for Pharmaceutical Manufacturers.[154] It calls for drug companies to establish voluntary compliance programs within the company.[155] Specifically, the program targets three risk areas: "(1) Integrity of data used . . . to establish payment; (2) kickbacks and other illegal remuneration; and (3) compliance with laws regulating drug samples."[156] The document is intended for drug companies to gain insight and foster adherence to relevant laws, especially involving federal health care programs.[157]

Another important business tactic widely impacting healthcare delivery involves off-label drug use.[158] Off-label use refers to the delivery of a pharmaceutical distinct from its approved labeling.[159] This can range from an

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thorship and Ghostwriting in Publications Related to Rofecoxib, 299 JAMA 1800, 1802 (2008) (describing Merck's use of ghostwriters with Vioxx).

150. FDA, Prescription Drug Promotion, http://www.fda.gov/NewsEvents/testimony/ucm115206.htm (last visited Apr. 17, 2010).

151. Barbara Mintzes, *Should Canada Allow Direct-to-Consumer Advertising of Prescription Drugs?*, 55 CAN. FAM. PHYSICIAN 131, 131 (2009).

152. PHRMA, CODE ON INTERACTIONS WITH HEALTHCARE PROFESSIONALS 2 (2008), *available at* http://www.phrma.org/files/attachments/PhRMA Marketing Code 2008.pdf.

153. *See* Press Release, PhRMA, PhRMA Revised Marketing Code Reinforces Commitment to Responsible Interactions with Healthcare Professionals (July 10, 2008), http://www.phrma.org/news_room/press_releases/phrma_code_reinforces_commitment_to_responsible_interactions_with_healthcare_professionals.

154. *See generally* OIG Compliance Program Guidance for Pharmaceutical Manufacturers, 68 Fed. Reg. 23,731, 23,731 (May 5, 2003).

155. *Id.*

156. *Id.* at 23,733.

157. *Id.* at 23,731.

158. *See* Randall S. Stafford, *Regulating Off-Label Drug Use—Rethinking the Role of the FDA*, 358 NEW ENG. J. MED. 1427, 1427 (2008), *available at* http://content.nejm.org/cgi/reprint/358/14/1427.pdf.

159. *Id.*

increased dose to a shortened duration of treatment to a novel use.[160] Once a drug is approved by the FDA, the actual use becomes part of the practice of medicine, and thus beyond the purview of the FDA.[161] Off-label drug use accounts for approximately twenty percent, with certain drug classes approaching seventy-five percent.[162] This use is considerable and has even landed a prominent physician in jail for unlawful promotion.[163]

IV. STATUTORY REGULATION OF DRUGS AND BIOLOGICS

Drugs, including biologics, are regulated primarily under federal legislation via the interstate commerce clause of the United States Constitution. Traditionally, health, safety, and welfare, the so called police powers, are reserved to the states. However, as drugs "substantially affect interstate commerce," their regulation is deemed a federal matter subject to federal purview.[164]

A. *Drug Regulation under the FDCA*

Federal drug regulation occurs primarily through the Federal Food, Drug, and Cosmetic Act (FDCA).[165] This Act was first legislated in 1938 in response to the tragic sulfanilamide incident and has since undergone a number of important revisions.[166] In part, the act prohibits the movement in inter-

160. *Id.*

161. *See id.*

162. *Id.*

163. Press Release, U.S. Attorney's Office, Eastern Dist. N.Y., Psychiatrist Charged with Conspiracy to Illegally Market the Prescription Medication Xyrem, Also Known as "GHB," for Unapproved Medical Uses on Behalf of its Manufacturer (Apr. 5, 2006), *available at* http://www.justice.gov/usao/nye/pr/2006/2006apr05.html; *see also* Alex Berenson, *Indictment of Doctor Tests Drug Marketing Rules*, N.Y. TIMES, July 22, 2006, at A1. Pfizer recently settled to pay $2.3 billion for fraudulent marketing which is "the largest health care fraud settlement" in history. News Release, U.S. Dept. of Health & Human Servs., Justice Department Announces Largest Health Care Fraud Settlement in Its History (Sept. 2, 2009), http://www.hhs.gov/news/press/2009pres/09/20090902a.html. The settlement included a felony plea to the FDCA and a billion dollar settlement under the civil False Claims Act. *Id.*

164. Gonzales v. Raich, 545 U.S. 1, 17 (2005) (citing NLRB v. Jones & Laughlin Steel Corp., 301 U.S. 1, 37 (1937)).

165. *See generally* Federal Food, Drug, and Cosmetic Act, § 1, 21 U.S.C. § 301 et seq. (2006).

166. For a nice history and overview on the regulation of drugs see Matthew J. Seamon, *Plan B for the FDA: A Need for a Third Class of Drug Regulation in the United States Involving a "Pharmacist-Only" Class of Drugs*, 12 WM. & MARY J. WOMEN & L. 521, 537–47 (2006).

state commerce of a new drug without an approved application.[167] Approval can arise from a New Drug Application (NDA), "paper NDA," abbreviated NDA, or Over-the-County (OTC) Monograph.[168]

Under the FDCA, a drug is defined as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease."[169] This means the intended use, via the labeling of a product, dictates its status. The FDCA further regulates drugs through its misbranding and adulteration provisions.[170] Adulteration refers, in part, to a drug product that is "filthy, putrid, or decomposed."[171] Misbranding involves a drug's label.[172] Any false or misleading labeling statements render the drug misbranded.[173] Drugs found to be adulterated or misbranded are subject to seizure by the FDA and other enforcement mechanisms.[174] The FDCA also authorizes the IND, which allows an unapproved drug to be researched.[175] Historically, a number of biologics have been approved solely under the FDCA, including insulin and human growth hormone.[176]

1. New Drug Application (NDA)

Under the FDCA, drugs require premarket clearance before they can be sold in the United States.[177] Drugs that appear to have a positive risk to benefit ratio are then sought for marketing approval.[178] This typically occurs through a New Drug Application (NDA), authorized under section 505(b)(1) of the FDCA.[179] The NDA is the comprehensive collection of data and knowledge on a drug product.[180] The goal of an NDA is to demonstrate to the FDA that a drug is safe and effective, the labeling is appropriate, and that

167. 21 U.S.C. §355(a) (2006).
168. *See* FDA, Small Business Assistance, *supra* note 115.
169. 21 U.S.C. § 321(g)(1)(B).
170. 21 U.S.C. §§ 342, 352.
171. 21 U.S.C. § 342(a)(3).
172. 21 U.S.C. § 352(a).
173. *Id.*
174. 21 U.S.C. § 334. Although the FDA maintains enforcement authority for civil, criminal, and administrative actions, they maintain a cooperative working relationship with the U.S. Department of Justice involving many criminal matters. *See* 21 U.S.C. § 335. In fact, section 335 authorizes the FDA to report criminal violations to said department. *Id.*
175. 21 U.S.C. § 355(i); 21 C.F.R. 312.23 (2009).
176. Andrew Wasson, *Taking Biologics for Granted? Takings, Trade Secrets, and Off-Patent Biologics*, 4 DUKE L. & TECH. REV. ¶ 9 (2005).
177. *See* 21 C.F.R. § 314.1; 21 U.S.C. § 355.
178. *See* 21 C.F.R. § 314.2.
179. *See* 21 U.S.C. § 355(b); 21 C.F.R. § 314.50.
180. *See id.*

the manufacturing ensures the drug's identity, strength, quality, and purity.[181] The NDA even includes a section on environmental impact.[182]

Drugs have to demonstrate safety and efficacy under a burden of substantial evidence.[183] They also have to submit preclinical data—animal pharmacology and toxicology—to demonstrate current good manufacturing practices, compliant product packaging and labeling, and follow postmarketing requirements including reporting known adverse effects.[184]

The NDA is assigned a Therapeutic Review Classification based on the importance of the drug, which dictates the FDA's timeline for review.[185] The FDA typically then utilizes an advisory committee to help evaluate the drug and make a non-binding recommendation as to approval.[186] Applications with deficiencies receive a "complete response letter" describing the agency's findings of concern.[187] Drugs suitable for approval can then be approved and licensed under the FDCA to move in interstate commerce as long as they are not adulterated or misbranded.[188] Any changes in indications, manufacturing procedures, labeling, dosage form, or dosing, require a supplemental application referred to as an NDA.[189]

B. *Biologics Defined*

Biologic drugs are large molecule products, typically proteins, derived from a living organism or one of its products and manufactured through a

181. 21 U.S.C. § 355(b); 21 C.F.R. § 314.50(b).

182. 21 C.F.R. § 314.50(d)(1)(iii).

183. 21 U.S.C. § 355(d).

184. *See* FED. TRADE COMM'N, EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION, at 6 (2009), *available at* http://www.ftc.gov/os/2009/06/P083901biologicsreport.pdf [hereinafter FTC 2009 REPORT]; 21 U.S.C. § 355(b)(1).

185. CTR. FOR DRUG EVALUATION AND RESEARCH, U.S. FOOD & DRUG ADMIN., MANUAL OF POLICIES AND PROCEDURES 6020.3 1, at (2007), *available at* http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm082000.pdf. Drugs that provide a "significant improvement compared to marketed products," receive priority review within six months, and remaining drugs are reviewed within a ten month time frame. *Id.* at 1–2; FDA, Fast Track, Accelerated Approval and Priority Review, http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/SpeedingAccesstoImportantNewTherapies/ucm128291.htm (last visited Apr. 17, 2010).

186. *See* FDA, Advisory Committees, http://www.fda.gov/AdvisoryCommittees/default.htm (last visited Apr. 17, 2010). The FDA identifies forty-nine advisory committees. *Id.*

187. 21 C.F.R. § 314.110(a) (2009).

188. *See* 21 C.F.R. § 314.105.

189. 21 C.F.R § 314.7(b). Supplemental applications are differentiated based on minor changes to be described in an annual report, moderate changes which require a thirty-day premarket notification to the FDA, and major changes which must be approved prior to distribution of the drug. 21 C.F.R § 314.7(a)–(c).

DNA or RNA pathway.[190] Biologics comprise a large and diverse group of products used in a myriad of diseases and conditions. Traditional drugs are small molecule products produced by chemical synthesis combining chemicals and reagents in inert reaction vessels.[191] These drugs are well-defined and thoroughly characterized; whereby biologics are typically less thoroughly characterized as they are derived from living materials, susceptible to environmental conditions and are of greater complexity.[192] Since biologics are protein based, they are typically administered via injection to bypass enzymatic destruction in the stomach, whereas drugs are typically administered orally.[193] Biologics generally have less stability than traditional drugs and often require refrigeration.[194]

Biologics are biochemically complex, exhibiting a primary structure (amino acid sequence), a secondary structure (disulfide bonding), tertiary structure (elaborate bending), and a quaternary structure (final aggregation of the compound).[195] Additionally, many of these products are glycosolated having multiple shapes called isoforms.[196] Thus, biologics exist in multiple conformations and may readily convert between each.[197] It is possible, in fact, that all possible variants of a biologic are not fully characterized.[198]

Manufacturing biologics is a highly sophisticated process, much different from traditional drugs.[199] Biologics often utilize a specific cell line and require precise and consistent manufacturing involving highly developed

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190. *See* Michael Kleinberg & Kristen Wilkinson Mosdell, *Current and Future Considerations for the New Classes of Biologicals*, 61 AM. J. HEALTH-SYS. PHARMACY 695, 697 (2004). In very basic terms a certain biologic (protein) is sought. *See id.* Scientists obtain the gene to code for the protein. *See id.* at 698. This gene is then inserted into a living system—typically bacteria, yeast or Chinese hamster ovary—which then produces the desired product, which then is highly purified. *See id.* at 699. Interestingly, the first recorded use of biological therapeutics involves the use of an antibiotic obtained from moldy soy in China, in 500 BCE, to treat boils. Philip E. Johnson, *Implications of Biosimilars for the Future*, 65 AM. J. HEALTH-SYS. PHARMACY S16, S16 (2008).

191. These drugs refer to typical organic-based drugs such as aspirin, Lipitor and Norvasc. *See* D.J.A. Crommelin et al., *Shifting Paradigms: Biopharmaceuticals Versus Low Molecular Weight Drugs*, 266 INTL. J. PHARMACEUTICS 3, 4 (2003).

192. *See* Kleinberg & Mosdell, *supra* note 190, at 696.

193. *See* A. Baumann, *Early Development of Therapeutic Biologics–Pharmacokinetics*, 7 CURRENT DRUG METABOLISM 15, 18 (2006).

194. Johnson, *supra* note 190, at S20.

195. *See* Crommelin et al., *supra* note 191, at 4.

196. *See id.* at 6.

197. *See* Janet Woodcock et al., *The FDA's Assessment of Follow-on Protein Products: A Historical Perspective*, 6 NATURE REVS. DRUG DISCOV. 437, 438 (2007).

198. *See id.*

199. Johnson, *supra* note 190, at S16. Amazingly, bioengineering dates back to 4000 BCE, where yeast fermentation was used to produce alcohol for festivity. *Id.*

fermentation processes and purification methods.[200] Even very slight deviations in the manufacturing process can result in an altered bioactivity changing the actions of the compound.[201] Impurities and contaminants pose serious threats and some may contain intrinsic infectious agents.[202]

The cloning technology required to manufacture biologics originated in the 1970s and is a highly complex and sequential process.[203] The first biologic approved was recombinant insulin (Humulin, Lilly), in 1982.[204] Since then more than 250 biologics have been approved and marketed in the United States.[205] These products range from botulinum neurotoxin for wrinkles,[206] to monoclonal antibody based therapies for colon cancer,[207] to vaccines for chicken pox,[208] to enzyme replacement therapy for Pompe disease.[209]

As biologics are rather complex molecules, they carry risks not typically associated with traditional drugs.[210] The most important of these risks is immunogenicity.[211] Immunogenicity refers to neutralizing antibody formation against a foreign substance, in this case, a biologic.[212] Biologics are inherently immunogenic because of their biochemical composition.[213] To

200. Felcone, *supra* note 10, at 26.

201. *See* Jeremiah J. Kelly & Michael David, *No Longer "If," but "When": The Coming Abbreviated Approval Pathway for Follow-on Biologics*, 64 FOOD & DRUG L.J. 115, 120 (2009).

202. *See* Woodcock et al., *supra* note 197, at 438.

203. Robert I. Roth & Nicholas M. Fleischer, *A Follow-on Biological Drug Is Not a Biogeneric: Lessons from Omnitrope and Valtropin*, 6 J. GENERIC MEDS. 237, 238 (2009). *See generally* Johnson, *supra* note 190 (for a concise review). In 1958, Frederick Sanger won the noble prize for his work in protein sequencing when he sequenced insulin. Frederick Sanger–Autobiography, NobelPrize.org, http://nobelprize.org/nobel_prizes/chemistry/laureates/1958/sanger-bio.html (last visited Apr. 17, 2010).

204. Thijs J. Giezen et al., *Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union*, 300 JAMA 1887, 1887 (2008).

205. *Id.*

206. *See* Botox Cosmetic Home Page, http://www.botoxcosmetic.com/hom.aspx (last visited Apr. 17, 2010).

207. Erbitux, http://www.erbitux.com/index.aspx (last visited Apr. 17, 2010).

208. Merck Vaccines: Varivax, http://www.merckvaccines.com/vaccines/vari/varivax.html (last visited Apr. 17, 2010).

209. The Successful Effort to Develop Myozyme for Pompe Disease at Genzyme FAQs, The Successful Effort to Develop Myozme and Bring New Hope for to Families Affected by Pompe Disease, http://www.genzyme.com/pompemovie/pompe-movie-faq.htm (last visited Apr. 14, 2010). This drug is based on the research of a father with "two children with Pompe disease." *Id.* The story is depicted in the movie, *Extraordinary Measures*. *Id.*

210. Giezen et al., *supra* note 204, at 1888.

211. *Id.*

212. *Id.*

213. *Id.*

confound the issue, biologics are almost universally injectable and thus pose increased immunogenic potential.[214] Immunogenicity tends to render a drug ineffective and may cause allergic type reactions that could be fatal.[215] Biologics may also pose an increased risk of infection and cancer compared to traditional drugs.[216] Traditional drugs may also be immunogenic, although the concern is that biologics pose a greater risk.[217]

It is important to differentiate biologics from gene therapy and other fields of biotechnology. Although these areas may ultimately merge, the current state of technology is separate and regulation involving gene therapy is at its infancy and beyond the scope of this paper.[218]

1. Biologic Regulation under Public Health Service Act

Biologics are a subset of drugs regulated primarily under Section 351 of the Public Health Service Act (PHSA) and part 600 of title 21 of the *Code of Federal Regulations*.[219] The PHSA was established in 1944 and served to revise and consolidate the existing public health legislation including the Biologics Control Act of 1902.[220] Under the PHSA, biologics are defined as "any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man."[221] Biologics further intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease are regulated as drugs and therefore subject to the requirements of the FDCA and the PHSA.[222]

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214. Scott Gottlieb, *Biosimilars: Policy, Clinical, and Regulatory Considerations*, 65 AM. J. HEALTH-SYS. PHARMACY S2, S5 (2008).

215. Giezen et al., *supra* note 204, at 1888.

216. *Id.*

217. *See id.*

218. *See* Johnson, *supra* note 190, at S19–20.

219. Public Health Service Act § 351, 42 USC § 262 (2006); 21 C.F.R pt. 600 (2009).

220. David M. Dudzinski & Aaron S. Kesselheim, *Scientific and Legal Viability of Follow-on Protein Drugs*, 358 NEW ENG. J. MED., 843, 844 (2008). In 1901, thirteen deaths of children by tetanus were traced back to a diphtheria antitoxin obtained from the blood of local horse named Jim. Linda Bren, *The Road to the Biotech Revolution: Highlights of 100 Years of Biologics Regulation*, FDA CONSUMER, Jan.–Feb. 2006, at 50, 51. At the same time, a similar tragedy occurred in New Jersey. *Id.* These events prompted Congress to regulate biologics with the passage of the 1902 Biologics Control Act, also known as the Virus-Toxin Law. *Id.*

221. 21 CFR § 600.3(h) (2009).

222. Gottlieb, *supra* note 214, at S3–S4.

Interestingly, biologics are regulated within both CBER and CDER.[223] Under the current regulatory framework, some "therapeutic biologic products" are reviewed and regulated by CBER, while others are reviewed by CDER.[224] Effective June 30, 2003, CDER regulates monoclonal antibodies and proteins for therapeutic use, which comprise a rather significant proportion of biologics.[225] CBER regulates cellular products, gene therapy, vaccines, allergenic extracts, blood and blood products, and certain fibrinolytics.[226] Drugs licensed under the PHSA are exempt from the licensing requirements of the FDCA.[227]

a. *Biologic Licensing Application*

Biologics are developed similarly to traditional drugs and are subject to the same rigors of pre-market clearance.[228] Their research and development follows a very similar pathway including preclinical evaluation and clinical testing involving Phase I, Phase II, and Phase III studies.[229] Biologics almost universally have some Phase IV requirements based on the anticipated risks in large-scale populations.[230]

Unlike traditional drugs, biologics are reviewed and approved under a Biologic License Application (BLA).[231] An approved BLA is analogous to an NDA and provides the legal authority to move a biologic in interstate commerce.[232] Generally speaking, a BLA is approved on the basis of safety, purity, and potency of a biologic.[233] Additionally, the application must con-

223. Due to "historical vagaries," a number of recombinant biologics were approved under an NDA and regulated by CDER. *See* Dudzinski & Kesselheim, *supra* note 220, at 844.

224. FDA, Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133463.htm (last visited Apr. 17, 2010); Drug and Biological Product Consolidation, 68 Fed. Reg. 38067, 38068 (June 26, 2003).

225. *See* FDA, Transfer of Therapeutic Products to the Center for Drug Evaluation and Research, *supra* note 224. These include such drugs as cytokines—e.g. interferons—and enzymes—e.g. thrombolytics. *See id.*

226. *Id.* These include such drugs as immunoglobulins and antivenims. *Id.*

227. *See* 42 U.S.C. § 262(j) (2006).

228. *See* Jessica R. Underwood, *What the EU Has That the US Wants: An Analysis of Potential Regulatory Systems for Follow-On Biologics in the United States*, 10 DEPAUL J. HEALTH CARE L. 419, 435 (2007).

229. *See id.* at 435–36.

230. *See id.* at 436.

231. 21 C.F.R. § 601.20 (2009).

232. *See* 21 C.F.R. § 601.20(b)(1), (d).

233. 21 C.F.R. § 601.20(c). New Drug Application (NDA) is predicated on safety, efficacy, and compliance with current good manufacturing practices. U. S. Food & Drug Admin., New Drug Application (NDA), http://www.fda.gov/Drugs/DevelopmentApprovalProcess/

tain data on chemistry, manufacturing, and controls; non-clinical pharmacology and toxicology; patent information; and labeling.[234] The requirements for approval of a biologic are often more challenging than traditional drugs since any small deviation in manufacturing can result in a significant impact on the bioeffectiveness, and the risk of unanticipated problems is a greater threat.[235]

V. GENERIC DRUG REGULATION / DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984

During the 1970s and 1980s, drug prices began to increase rather dramatically.[236] To complicate the issue, the wide availability and acceptance of generic drugs was not to be found.[237] Most states do not substitute laws for the pharmacist, and generic manufacturers had to undergo costly and time-consuming full-scale studies to gain approval.[238] Moreover, generic companies had to wait for a patent to expire before ever commencing research and production, thus effectively extending the innovators patent.[239] Suffice it to say, the generic drug industry was not bountiful and brand companies enjoyed lengthy patent protections.

Seeking to streamline this concern, increase the availability and use of generic drugs, all while protecting innovation and patents, Congress passed the Drug Price Competition and Patent Term Restoration Act of 1984.[240] This landmark legislation, commonly referred to as the Hatch-Waxman Amendments to the FDCA,[241] sought to strike a balance between two important competing interests: increased availability of generic drugs and en-

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HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm (last visited Apr. 17, 2010). Potency of biologics is essentially synonymous with the term efficacy as it relates to drugs. *See* 21 C.F.R. § 601.20(c).

234. *See* 21 C.F.R. § 601.20.

235. *See* Underwood, *supra* note 228, at 436.

236. *See* David Pryor, Commentary, *A Prescription for High Drug Prices*, 9 HEALTH AFF. 101, 101–02 (1990).

237. *See id.* at 102–03.

238. *See* FED. TRADE COMM'N, GENERIC DRUG ENTRY PRIOR TO PATENT EXPIRATION: AN FTC STUDY 4 (2002), *available at* http://www.ftc.gov/os/2002/07/genericdrugstudy.pdf [hereinafter FTC 2002 STUDY].

239. Satish Chintapalli, *Excessive Reverse Payments in the Context of Hatch-Waxman*, 10 N.C. J. L. & TECH. 381, 388 (2009).

240. *See generally* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2006)).

241. Named after Republican Senator Orrin Hatch (Utah) and Democrat Congressman Henry Waxman (California). *See* Gerald J. Mossinghoff, *Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*, 54 FOOD & DRUG L.J. 187, 187 (1999).

hanced patent protection for branded products.[242] The Act consists of two titles. Title I amended the FDCA and established an abbreviated approval pathway for generic drugs under an Abbreviated New Drug Application (ANDA).[243] It also provides exclusivity for brand drug approvals.[244] Title II authorizes the extension of patent terms for approved new drug products.[245] Brand drugs receive "an extension term equal to one-half of the time of the investigational new drug (IND) period . . . plus the NDA period . . . [with a] maximum extension [of] five years and the total market exclusivity time cannot exceed fourteen years."[246] Hatch-Waxman requires all drug applications under the FDCA to file patent information with the FDA.[247] This way, the agency has clear direction in granting exclusivity for brand drugs and approving generic drugs. Hatch-Waxman only applies to drugs and the FDCA, and did not include provisions to allow for an abbreviated approval pathway under section 351 of the PHSA.[248]

In order to fully appreciate Hatch-Waxman, one must grasp the drug approval process for generics. There are currently three mechanisms by which a generic drug can enter the prescription market when a patent expires on a brand product—NDA, ANDA, and Paper NDA. All three are available under the FDCA.[249] The use of an NDA for a generic drug is not commonly used, based on the cost and complexity of the information included. The ANDA is a much more efficient and cost effective route and is the most commonly employed pathway. Another abbreviated approval mechanism is the Paper NDA, more technically referred to as 505(b)(2) approval. The Paper NDA is similar to an NDA but allows the FDA to rely on published data and previously determined assessments of safety and efficacy in its approval. Although a paper NDA can apply to a generic drug, it is typically reserved for minor changes of an existing drug, such as formulation or dosing.[250]

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242. *See* Drug Price Competition and Patent Term Restoration Act of 1984 § 101.

243. *Id.* Before the approval of this act, generic drugs were required to undergo the same rigorous clinical trials as branded drugs. FTC 2002 STUDY, *supra* note 238, at 3. These were typically large scale randomized controlled efficacy and safety trials. *Id.* Needless to say, this research was cumbersome, costly, and complex. It was also unnecessary.

244. *See* Drug Price Competition and Patent Term Restoration Act of 1984 § 101.

245. *Id.* § 201.

246. Mossinghoff, *supra* note 241, at 190 (1999).

247. *See id.* at 189.

248. Dudzinski & Kesselheim, *supra* note 220, at 845.

249. 21 U.S.C. § 355(6)(j) (2006).

250. Gregory J. Glover, *The Influence of Market Exclusivity on Drug Availability and Medical Innovations*, 9 AM. ASS'N PHARMACEUTICAL SCI. J. E312, E313 (2007).

A. *Generic Drugs*

The generic drug industry is a true boon by all social accounts.[251] Generic drugs represent almost seventy percent[252] of all prescriptions filled, yet account for only sixteen percent of the expenditure.[253] The average brand drug costs $120 per month and the average generic drug costs less than $35.[254] Over the past ten years, the United States healthcare has saved approximately $700 billion dollars through the use of generic drugs.[255] Generic utilization occurs as follows. Physicians can prescribe a brand drug or a generic.[256] If the prescriber writes out a prescription for a brand drug, the pharmacist typically substitutes a generic, if available.[257] In fact, under Medicare law, pharmacists are typically required to substitute.[258] Alternatively, many insurance companies may only pay for a generic if available.[259] If a patient insists on a brand product or there is no generic available, the patient receives and pays for the brand drug.[260]

Despite the considerable impact associated with generic drugs, the economic framework remains somewhat musing and the full cost savings is often delayed and slow to materialize.[261] The first generic to market is typically priced at about ninety-four percent of the brand drug's price, thus offering a very nominal cost-savings.[262] It is not until a second generic comes to mar-

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251. *See* FTC 2002 STUDY, *supra* note 238, at 9.

252. This is "up from 19 percent in 1984 when Hatch-Waxman was" approved. *Id.* at i.

253. Facts at a Glance, Generic Pharmaceutical Association, http://www.gphaonline.org/about-gpha/about-generics/facts (last visited Apr. 17, 2010).

254. *Id.*

255. Press Release, Congressman Frank Pallone, Jr., Pallone Statement at Health Hearing on Follow-On Biologic Drugs 2 (June 11, 2009), *available at* http://energycommerce.house.gov/Press_111/20090611/pallone_open.pdf.

256. DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF INSPECT. GEN., GENERIC DRUG UTILIZATION IN THE MEDICARE PART D PROGRAM 5 (2007).

257. *See id.* "Generic drug substitution is only possible when a health care provider prescribes a multisource drug (i.e., a brand name multisource drug or its associated equivalent)." *Id.*

258. *See id.* at 4.

259. *See id.* at 3.

260. *See* DEP'T OF HEALTH & HUMAN SERVS., OFFICE OF INSPECT. GEN., *supra* note 256, at 3.

261. *See* FDA, Generic Competition and Drug Prices, http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm129385.htm (last visited Apr. 17, 2010).

262. *Id.* Although this seems outrageous, it is actually quite logical. When a first generic comes to market, insurers almost always require the generic drug over the brand drug, thus significant market share is almost guaranteed. Nevertheless, once a second generic comes to market, the less expensive product receives the great lion's share of market push, thus poten-

ket that a substantial, fifty percent cost savings is seen, and it takes approximately seventeen generics competing until a ninety percent cost-savings is realized.[263]

B. *Abbreviated New Drug Application (ANDA)*

Hatch-Waxman codified an abbreviated approval pathway for generic drugs via 505(j) of the FDCA.[264] The general requirements of an ANDA are chemistry, manufacturing, labeling, and proof of bioequivalence.[265] Collectively this is termed Therapeutic Equivalence.[266] The ANDA is considered abbreviated because it does not require proof of preclinical or clinical data, both of which are required in an NDA.[267] Since generic drugs do not require this information, the cost to bring a generic to market is greatly reduced. Instead of relying on clinical data, the sponsor for a generic drug has to prove bioequivalence to the brand drug.[268] Bioequivalence is established when "the rate and extent of absorption of the test drug do not show a significant difference from the rate and extent of absorption of the reference drug."[269] This is essentially a surrogate marker used to demonstrate safety and efficacy of the drug. In place of preclinical data, the sponsor submits only a section on chemistry allowing the FDA to rely on the reference listed drug approval as underpinning.[270]

An ANDA also has to include information on patents. The generic sponsor must "certify" the status of the patent they are copying.[271] There are four types of certification available.[272] Paragraph I certifies the challenged drug has not been patented.[273] Paragraph II certifies the patent has already expired on said drug.[274] Paragraph III certifies the date the patent will expire

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tially squeezing out the original generic if it does not lower its price. This window of opportunity is often short lived and not assured, so generic companies use it to maximize profit.

263. *Id.*

264. *See* Federal Food, Drug, and Cosmetic Act § 505(j), 21 U.S.C § 355(j) (2006).

265. *Id.*

266. *See id.*

267. *See* 21 U.S.C. § 355(i)–(j).

268. 21 U.S.C. § 355(j).

269. DEP'T OF HEALTH & HUMAN SERVS., APPROVED DRUG PRODUCTS, *supra* note 14, at v. The "[m]ethods used to define bioequivalence can be found in 21 C.F.R [§] 320.24 [2010] and include (1) pharmacokinetic (PK) studies, (2) pharmacodynamic (PD) studies, (3) comparative clinical trials, and (4) in-vitro studies." *Id.*

270. 21 U.S.C. § 355(j)(9).

271. 21 U.S.C. § 355(j)(2)(A)(vii).

272. *Id.*

273. 21 U.S.C. § 355(j)(2)(A)(vii)(I).

274. 21 U.S.C. § 355(j)(2)(A)(vii)(II).

on said drug and assures that the generic drug will not go on the market until that date passes.[275] Paragraph IV certifies that the patent is not infringed or is invalid.[276]

Paragraph IV certifications are the most controversial and contentious. The first generic to successfully file Paragraph I certification receives a 180-day marketing exclusivity.[277] This very clever provision is intended to promote immediate filing of an ANDA by creating a monopoly within a monopoly for the first generic approved. This incentive appears to be very intelligently calculated and provides sufficient reward to increase generics without too much hindrance on the overall market. Paragraph IV certifications receive a lot of press and have spawned a number of tactical business practices and legal maneuverings.[278]

The filing of a Paragraph IV certification also triggers a peculiar thirty-month stay provision preventing the generic drug to market.[279] A generic company that files an ANDA must notify the FDA and the brand company who then has forty-five days to file an infringement action, if so desired.[280] If no suit is filed and the application is complete and approvable, the FDA can license the drug for immediate market.[281] If the brand company does file an infringement action, the FDA stays "approval of the ANDA until the earliest of: 1) the date the patent[] expire[s]; 2) a final determination of non-infringement or patent invalidity by a court in the patent litigation; or 3) the expiration of 30 months from the receipt of notice of the [P]aragraph IV certification."[282] Practically speaking, by simply filing an infringement action, the brand company receives a thirty-month stay of approval of the generic; the theoretical approximate of the time to litigate the matter. Amazingly, two and a half years of additional exclusivity comes with low risk and nominal costs—a noticeable incentive. This automatic stay frustrates the system and further increases the gaming strategy employed in drug development.

275. 21 U.S.C. § 355(j)(2)(A)(vii)(III).
276. 21 U.S.C. § 355(j)(2)(A)(vii)(IV).
277. FTC 2002 STUDY, *supra* note 238, at 7; *see* 21 U.S.C. § 355(j)(5)(B)(iv)(I).
278. *See, e.g.*, ParagraphFour.com, Paragraph Four Explained, The Generic Approval Process, http://www.paragraphfour.com/explained/process.html (last visited April 17, 2010).
279. *Id.*
280. *Id.*
281. *See id.*
282. FTC 2002 STUDY, *supra* note 238, at 39.

C. *Paper NDA and the Case of Omnitrope®*

In addition to 505(j) approval with an ANDA, Hatch-Waxman also authorizes 505(b)(2) pathway for abbreviated approval, the so-called paper NDA.[283] This application allows for a sponsor to rely upon previously published literature for certain aspects of the application, including the FDA's determination of safety and efficacy.[284] Data on the reference listed drug is then used for the remaining requirements such as pharmacology and toxicology.[285] Drugs approved under a paper NDA are not necessarily substitutable for the comparator product and not AB listed in the Orange Book.[286] The paper NDA is considered a potential source of approval for a generic biologic, although the impediments seem overwhelming and the framework is not intended to regulate such actions and has never been used.[287] Technically speaking, there is no paper BLA and the authority for approval of a generic biologic under the current regulatory system is uncertain.[288]

Interestingly, the paper NDA has been used to approve one biologic, despite vigorous opposition and extensive legal wrangling.[289] On May 30, 2006, the FDA approved Omnitrope®[290] for marketing, despite a citizen's petition from Pfizer, Biotechnology Industry Organization, and Genentech urging otherwise.[291] Omnitrope® was approved, in part, through reliance of the FDA's determination of safety and efficacy of the reference listed drug,

283. *See* 21 U.S.C. § 355(b)(2), (j); Glover, *supra* note 250, at E313.

284. Michael P. Peskoe, *Paper NDAs and the Drug Price Competition Act: A Last Hurrah,*? 40 FOOD DRUG COSM. L.J. 323, 323 (1985); *see also* Letter from Steven K. Galson, Dir., Ctr. for Drug Evaluation & Research, to Kathleen M. Sanzo et al., Counsel for Petitioners 5 (May 30, 2006), *available at* http://www.fda.gov/ohrms/dockets/dockets/04p0231/04p-0231-pdn0001.pdf [hereinafter Letter from Steven K. Galson] (describing the practice of a paper NDA for drug approval).

285. *See* FTC 2002 STUDY, *supra* note 238, at 5.

286. LIONEL D. EDWARDS ET AL., PRINCIPLES AND PRACTICE OF PHARMACEUTICAL MEDICINE 383 (2007).

287. *See* Gottlieb, *supra* note 214, at S4.

288. *See* Donald E. Segal et al., *Regulatory Pathway for "Biosimilar" Products Debated,* LEGAL BACKGROUNDER (Wash. D.C.), Feb. 2007, at 1, 2.

289. *See id.*

290. Growth Hormone Deficiency Treatment: Omnitrope, Sandoz, http://www.omnitrope.com/omnitrope/index.html (last visited April 17, 2010). Omnitrope is a recombinant human growth hormone manufactured by Sandoz. *Id.* The innovator product is Genotropin, marketed by Pfizer, Inc. Genotropin Official Site-Human Growth Hormone, http://www.genotropin.com/content/Index.aspx (last visited April 17, 2010).

291. Letter from Steven K. Galson, *supra* note 284, at 1; FDA, Drug Details, Omnitrope, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails (last visited April 17, 2010).

Genotropin manufactured by Genetech, approved under an NDA.[292] FDA review found the drug was "sufficiently similar . . . to warrant [such] reliance" despite strong protest.[293] The application also included clinical data obtained by Genentech.[294] The FDA found a relative lack of complexity of the hormone and the availability of sufficient analytical techniques to approve the drug.[295] The FDA was clear this route of approval would not apply to biologics licensed under the PHSA or to products lacking a well-documented history of use.[296]

D. *Exploitation of Hatch-Waxman*

Practically speaking, Hatch-Waxman accomplished its aim. By most, if not all accounts, Hatch-Waxman increased access to generic drugs while providing sufficient protection and incentives for brand companies to continue to be innovative. However, like most if not all legislation, Hatch-Waxman is riddled with loopholes that have undermined some of its intent and has been subject to exploitation and abuse by brand companies seeking to maintain patent protection and prevent competition.[297] The legality of many of these strategies is made on a case-by-case basis and a number of settlements and decrees have occurred.[298]

The loopholes center around two provisions of the Paragraph IV certification: 180-day exclusivity and thirty-month stay.[299] Brand company manipulation of the 180-day exclusivity center around payments to generic companies not to market and the manufacturer of so called, "authorized generics."[300] Brand companies have been accused of filing baseless infringement actions to trigger the thirty-month stay provision and even file inequitable patent applications to delay market entry.[301] Lastly, brand companies can delist a patent after successful Paragraph IV certification to cause recertifica-

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292. *See* Segal et al., *supra* note 288, at 2. Genotropin was approved under a NDA and not a BLA although biochemically it is a biologic drug. FDA, Drug Details, Genotropin, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist (last visited April 17, 2010).

293. Letter from Steven K. Galson, *supra* note 284, at 8.

294. *See* Gottlieb, *supra* note 214, at S4.

295. *See* Dudzinski & Kesselheim, *supra* note 220, at 845.

296. *Id.*

297. FTC 2002 STUDY, *supra* note 238, at 39–40.

298. *See id.* at 16–17.

299. Avery, *supra* note 16, at 179.

300. *Id.* at 181.

301. *Id.* at 179–80.

tion under Paragraph I and the subsequent loss of exclusivity by the generic.[302]

The FTC has investigated a number of agreements not to compete between a brand company about to lose patent protection and the generic company awarded 180-day exclusivity.[303] These "pay for delay" agreements often involve a "reverse payment," whereas the brand company simply pays the generic company to not compete during the exclusivity period.[304] Interestingly, courts have been inconsistent as to the legality of this practice and some "pay for delay settlements" have been deemed legal.[305] The Sixth Circuit has ruled that reverse payments are a per se violation.[306] Meanwhile, the Eleventh Circuit approaches the issue using an analysis somewhere between per se and rule of reason.[307] Using a three part analysis the court looks to "(1) the scope of the exclusionary potential of the patent; (2) the extent to which the agreements exceed that scope; and (3) the resulting anticompetitive effects."[308]

Authorized generics refer to drug products manufactured by a brand company, identical to the brand product, but sold—i.e. authorized—as a generic.[309] The brand company can either sell the drug directly or license it to another company to label and sell.[310] Brand companies often introduce authorized generics during the 180-day exclusivity period as a first generic.[311] Although this clearly undermines the intent of Hatch-Waxman, is anticompetitive, and diminishes the incentive for generic companies to compete, it appears fully legal.[312] To date, the courts have upheld the legality of authorized generics through two appellate cases.[313] In fact, the United States Court of Appeals, District of Columbia Circuit, affirmed the decision to not even hear a citizen's petition made by a generic company, Teva.[314] Additionally, the United States Court of Appeals, Fourth Circuit, found no legal sufficiency to

302. *Id.* at 198.
303. *See* FTC 2008 REPORT, *supra* note 25.
304. Avery, *supra* note 16, at 181.
305. FTC 2009 REPORT, *supra* note 184, at i.
306. *In re* Cardizem CD Antitrust Litig., 332 F.3d 896, 908 (6th Cir. 2003).
307. *See* Valley Drug Co. v. Geneva Pharm., Inc., 344 F.3d 1294, 1311 & n.27 (11th Cir. 2003).
308. Schering-Plough Corp. v. FTC, 402 F.3d 1056, 1066 (11th Cir. 2005).
309. John M. Rebman, *Dr. Strange Drug, or: How I Learned to Stop Worrying and Love Authorized Generics*, 12 DEPAUL J. HEALTH CARE L. 159, 159 (2009).
310. *Id.*
311. *Id.* at 160.
312. *See id.* at 160, 181.
313. *See* Teva Pharm. Indus. Ltd. v. Crawford, 410 F.3d 51, 55 (D.C. Cir. 2005); Mylan Pharms. Inc., v. FDA, 454 F.3d 270, 276–77 (4th Cir. 2006).
314. *Teva Pharm. Indus. Ltd.*, 410 F.3d at 51, 55.

disallow the entry of an authorized generic by the NDA holder as they were within their statutory right.[315]

The thirty-month stay provision of Hatch-Waxman has been a real lure for brand companies, who have in turn sought inventive ways to trigger the stay.[316] A number of these techniques have been tried in court. For example, in the case of *In re Neurontin Antitrust Litigation*,[317] Pfizer, the brand manufacturer of Neurontin, was accused of filing sham litigation against the generic company, submitting false and fraudulent patents for inclusion in the Orange Book, and misconduct of patent prosecutions to impair competition.[318] In *Aventis Pharmaceuticals v. Amphastar Pharmaceuticals, Inc.*,[319] the court found incontrovertible evidence of inequitable conduct by the brand company with intent to deceive the U.S. Patent and Trademark Office in failing to disclose information in a patent application.[320]

The FTC stands in strong opposition to tactics aimed at undermining the integrity of Hatch-Waxman.[321] In fact, in 2008 the Commission issued a report detailing these practices, describing their anti-competitive effects.[322] The report was instrumental to changes in the original act that helped close some of the loopholes at the time. Additional legislation has been proposed to further close loopholes, but the system still remains open to manipulation and exploitation.[323]

The transcendent value of Hatch-Waxman is grounded on its impact on competition and, ultimately, drug prices. Although not perfect, the Act spawned an entire generic drug industry, while maintaining and rewarding innovation, which is no easy task.

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315. *Mylan Pharms.*, 454 F.3d at 276–77.

316. *See, e.g.*, FTC 2009 REPORT, *supra* note 184, at 57, 71.

317. No. 02-1390, 2009 WL 2751029 (D.N.J. Aug. 28, 2009).

318. *Id.* at *1, *4; *see* FTC 2002 STUDY, *supra* note 238, at 40.

319. 525 F.3d 1334 (Fed. Cir. 2008).

320. *Id.* at 1349.

321. *See* FTC 2008 REPORT, *supra* note 25; s*ee also* John R. McNair, Note, *If Hatch Wins, Make Waxman Pay: One-Way Fee Shifting as a Substitute Incentive to Resolve Abuse of the Hatch-Waxman Act*, 2007 U. ILL. J.L. TECH. & POL'Y 119, 126.

322. FTC 2008 REPORT, *supra* note 25, at 1.

323. For example, the Preserve Access to Affordable Generics Act (S. 369) prohibits generic companies from entering into agreements with brand companies to delay or cease from offering a generic option to the market. *See* PRESCRIPTION ACCESS LITIGATION FACT SHEET: THE PRESERVE ACCESS TO AFFORDABLE GENERICS ACT (S. 369)/ THE PROTECTING CONSUMER ACCESS TO GENERIC DRUGS ACT OF 2009 (H.R. 1706), July 22, 2009, http://www.prescriptionaccess.org/docs/Fact Sheet HR 1706 S369.pdf [hereinafter FACT SHEET: H.R. 1706/S. 369].

VI. CURRENT STATE OF GENERIC BIOLOGICS

Hatch-Waxman established a mechanism for generic drugs in the United States.[324] However, this act did not predict the role of biologics and a void was created. Meanwhile biologics, constitute a rising market share, and as patents continue to issue and expire, the need to substitute products in attempted cost-savings is a major policy concern. In the aughts, there were a number of failed attempts to regulate generic biologics; however, each measure was systematically defeated in Congress.[325]

In June 2009, the Federal Trade Commission released a comprehensive analysis on generic biologics.[326] The report found that competition between a biologic and its generic counterpart is more likely going "to resemble brand-to-brand competition, rather than [the traditional] brand-to-generic competition," because of the cost and complexity of bringing a generic biologic to market.[327] The report claimed that even in the presence of a generic biologic, the brand product would retain seventy to ninety percent of its market share, which is quite different than the current system, where erosion is immediate and glaring.[328] The report further asserted generic biologics would provide a cost-savings of approximately ten to thirty percent.[329] Overall, the report is clear that existing incentives provided for in Hatch-Waxman are sufficient for biologics, signifying that anything longer than five years of exclusivity will be anticompetitive.[330]

A. *Generic Biologics Defined*

The BPCIA defines a generic biologic as "a biological product approved under an abbreviated application for a license of a biological product that relies in part on data or information in an application for another biolog-

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324. *See* Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 (2006)).

325. *See, e.g.*, Access to Life Saving Medicine Act, H.R. 1038, 110th Cong. (2007); Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. (2007); Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. (2007); Pathway for Biosimilars Act, H.R. 5629, 110th Cong. (2008).

326. *See* FTC 2009 REPORT, *supra* note 184.

327. *Id.* at iii.

328. *Id.* at v.

329. *Id.* at v. The Congressional Budget Office estimates that generic biologics will be priced at a twenty to twenty-five percent reduction initially and increase to forty percent by the fourth year. CONG. BUDGET OFFICE, COST ESTIMATE: S. 1695, BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2007 7 (June 25, 2008), *available at* http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf [hereinafter CONG. BUDGET OFFICE, COST ESTIMATE].

330. FTC 2009 REPORT, *supra* note 184, at 57.

ical product licensed under section 351 of the Public Health Service Act. "[331] Biosimilarity is defined as a product "highly similar to the reference product notwithstanding minor differences in clinically inactive components; and there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency.[332]

Technically speaking, generic drugs refer to products manufactured without trademark protection.[333] Scientifically speaking, the term has come to mean a drug that has the same dosage, safety, strength, route of administration, quality, performance, and intended use as a brand drug—essentially an exact copy.[334] A generic drug is considered an identical copy to a brand drug with an associated cost-savings.[335]

Many claim the term "generic biologic" is a fallacy and inappropriate to use.[336] It is claimed that independently manufactured biologics should not be considered identical to each other based on a number of manufacturing variances and resulting subtleties.[337] Biologics are manufactured in living systems and fluctuations inevitably occur.[338] Instead, these copies are only considered *similar* and *follow-on* to a brand drug.[339] Accordingly, the choice term represents a meaningful characterization of the issue and driver of some of the legal, social, and scientific discussions.

Developing a generic biologic involves identifying the target drug, establishing duplicative or similar methods of production and product characterization to validate similarity. Generic biologics are referred to by a myriad of terms including: biosimilars, biogenerics, follow-on biologics, follow-on proteins, and subsequent entry biologics (SUB). There is no officially accepted scientific nomenclature, although the term biosimilars appears to have become vernacular in the United States with the passage of the BPCIA. Biosimilar is the preferred term in Europe, whereas Canada utilizes SUB to refer to these products. An all encompassing and adequate term may not exist.

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331. Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 3139(a)(2), 124 Stat. 119 (2010).

332. *Id.* § 7002(b).

333. *See* FDA, FACTS ABOUT GENERIC DRUGS (2009), http://www.fda.gov/downloads/Drugs/EmergencyPreparedness/BioterrorismandDrugPreparedness/UCM134015.pdf.

334. *Id.*

335. *Id.*

336. *See, e.g.*, G. Gastl et al., *ASHO Position Paper on Biosimilars*, 2 MAG. EUR. MED. ONCOLOGY, 2009, at 232.

337. EUROPEAN MEDS. AGENCY (EMEA), COMM. FOR MEDICINAL PRODS. FOR HUMAN USE, GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS 4 (Oct. 30, 2005), *available at* http://www.ema.europa.eu/pdfs/human/biosimilar/043704en.pdf [herinafter EMEA 2005].

338. Gottlieb, *supra* note 214, at S4.

339. *See id.* at S2.

Nevertheless, for the sake of discussion, generic biologic may be appropriately defined as a biological drug product with the same biochemical structure and function as a trademarked product with equivalent purity, potency, and safety.

1. Challenges with Generic Biologics

The primary goal of generic biologics involves product safety.[340] As with all drugs, safety is paramount and the production of an equivalent product with an equivalent safety profile is essential. The practical goal, meanwhile, is to establish a system that supports substitution of the generic biologic at the pharmacy level with an associated cost-savings to the payor.[341]

Based on the complex biochemical nature of biologics, the creation of an equivalent generic poses a myriad of challenges before it can be widely produced and accepted. First, there must be a system to define and establish structural equivalency. Replication must be feasible based on the patent and there must be a method to characterize the product as equivalent. Next, there must be a method to assure functional equivalency of products, namely safety, purity, and potency. Practitioners and patients must then have confidence in the substitution of these products and payors must realize an actual cost-savings.

The requirements for establishing equivalency are going to vary by the drug involved.[342] While certain classes of biologics may only require general guidelines to establish equivalency, other, more complex agents may require very specialized and particular approaches to demonstrate both structural and functional equivalency.[343] The establishment and inclusion of Compendium standards should be sought.[344] Any variances determined will then have to be supported by evidence of no effectual difference for equivalency to be established.[345]

Structurally, generic biologics are thought to be extremely difficult to produce an exact replica, unlike small molecule generics which are rather easy to replicate and produce.[346] Differences in cell lines, manufacturing practices, temperature, pH, finishing and storage conditions, and protein ag-

340. Gottlieb, *supra* note 214, at S3.

341. *See id.*

342. *See* Crommelin et al., *supra* note 191, at 14.

343. *See id.*

344. *See* Emily Shacter, Follow-on Biologics Workshop: Scientific Issues in Assessing the Similarity of Follow-on Protein Products (2005), http://www.biosimilarstoday.com/Shacter.pdf.

345. *See* Crommelin et al., *supra* note 191, at 14.

346. *See* Woodcock et al., *supra* note 197, at 438.

gregation, can all affect product structure.[347] Another challenge involves analyzing these products for structural equivalency.[348] Traditional drugs are considered easy to characterize, whereas characterization of biologics is extremely difficult.[349] Crystal studies only capture the current confirmation of a biologic, which can exist in multiple states.[350] Highly advanced analytical techniques such as X-ray crystallographic diffraction, MRI, and reversed-phase high-performance liquid chromatography are going to be required to establish structural equivalence, if at all possible under the current state of technology.[351] Orthogonal methods will be needed and multiple techniques may be required.[352]

Batch to batch variability inevitably occurs with biologics and impurities may be present.[353] Brand companies have argued information on variability is a trade secret and confidential commercial information is available only to the FDA.[354] They argue that any use of protected information would require the FDA to pay just compensation under the Fifth Amendment's Takings Clause.[355]

Establishing functional equivalency will also pose some challenges. Even though we have reliable biomarkers to assess equivalence with most drugs, the physical complexity of biologics and the various confirmations of isoforms are problematic.[356] For instance, a biologic could have the same response in a pharmacodynamic measure such as blood pressure with its comparator, but have other, unanticipated responses, i.e. side effects, based on its folding characteristics and the way it binds to a certain receptor.[357]

As immungenecity is a concern with all drugs, it becomes a greater concern with generic biologics, especially when interchangeability is consi-

347. *See* Crommelin et al., *supra* note 191, at 14.

348. *See id.*

349. Gottlieb, *supra* note 214, at S4.

350. *See* Crommelin et al., *supra* note 191, at 6.

351. *See The Quality and Purity of Retacrit(R) Was Readily Demonstrated and Was Shown to Maintain Haemoglobin Levels in Patients with Chronic Kidney Disease*, MEDICAL NEWS TODAY, May 27, 2009, http://www.medicalnewstoday.com/articles/151513.php.

352. *See* Shacter, *supra* note 344.

353. *See* Crommelin et al., *supra* note 191, at 14.

354. Letter from Kathy J. Schroeher, Assoc. Gen. Counsel, Johnson & Johnson, to Division of Dockets Management, Food & Drug Admin., Dep't of Health & Human Servs., (July 1, 2004), *available at* http://www.fda.gov/ohrms/dockets/dockets/04p0171/04p-0171-c000002-01-vol1.pdf.

355. *See* U.S. CONST. amend. V, XIV. Specifically, information on chemistry, manufacturing, and controls are believed to be widely protected. *See* Letter from Kathy J. Schroeher, *supra* note 354, at 6 & n.9.

356. *See* Crommelin et al., *supra* note 191, at 14.

357. Gottlieb, *supra* note 214, at S4.

dered.[358] Since biologics are complex proteins, they can elicit a number of immune responses, depending on a number of factors.[359] Although very similar, two inexact biologics can elicit very different immune responses.[360]

Overall, biologics represent a very diverse complexity of products, and thus many of these considerations do not apply equally and the FDA will have to deal with many of these issues on a case-by-case basis, at least initially.[361] The FDA has not yet developed a formal system to evaluate equivalence and is going to have to have an open approach, likely involving a consensus of the professional and scientific communities.[362] Only when structural and functional equivalencies are truly established with confidence, can we begin talking about product substitution and cost-savings.

The FDA will have to compile some system that supports substitution for biologics, like the Orange Book's AB rating system for conventional drugs.[363] Once equivalency is established, it is likely that physicians and pharmacists will be amenable to product substitution as the current system of generics has demonstrated. Legislators can then move to require substitution. Opposition is expected with lobbying efforts by the Biotechnology Industry Organization (BIO), and PhRMA, the biologic and drug trade associations respectively, leading the way. Payors, concerned with the bottom line, will likely push for substitution, helping advance the system and promote acceptance.

The cost of developing a generic biologic is large, estimated at $100-$200 million; much greater than a traditional generic drug.[364] There will be a need for particular cell lines and highly specialized manufacturing processes, the availability of which may prove a tough find. A full biogeneric industry does not currently exist as the need has not arisen.[365] The review process is going to be extremely challenging and may ultimately require a significant amount of data, and may thus be costly to the generic company.[366] Nevertheless, once the regulatory framework is established, companies will step forward as it remains a highly lucrative industry and drug prices should be expected to fall over time.

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358. See J.L. Prugnaud, *Similarity of Biotechnology-Derived Medicinal Products: Specific Problems and New Regulatory Framework*, 65 BR. J. CLIN. PHARMACOL. 619, 620 (2007).

359. *See* Crommelin et al., *supra* note 191, at 11.

360. *See id.*

361. *See id.* at S4, S7.

362. Richard G. Wenzel, *Introduction*, 65 AM. J. HEALTH SYST. PHARM. S1, S1 (2008).

363. *See id.*

364. Posting of Maggie Mahar, The Battle over Biologics Begins, to http://www.healthbeatblog.com/2009/06/the-battle-over-biologics-begins-.html (June 26, 2009).

365. *See* Engelberg et al., *supra* note 5, at 1917–18.

366. *Id.* at 1918.

B. *International Regulatory Approach*

Australia does not categorize biologics separate from drugs, so their position is less problematic.[367] Canada issued a Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs) and Related Documents on January 30, 2008.[368] The draft document was revised and republished on March 27, 2009, and is amidst review and further development.[369]

Canada does not plan on establishing a new regulatory framework, but will instead rely upon its existing statutory authority for Health Canada to review and approve these products.[370] SEBs will be analyzed on a case-by-case basis and reviewed as new drugs.[371] They will not follow the abbreviated approval pathway available for generic drugs nor be substitutable.[372] They will have no exclusivity, per se.[373] Nevertheless, the appeal is that the submission can rely, "in part, on prior information regarding the authorized innovative biologic drug in order to present a reduced clinical and non-clinical package."[374] Additionally SEBs can be submitted for innovator biologics not approved in Canada.[375]

Overall, the Canadian approach appears to be a reasonable approach to the issue. As technology further advances, costs continue to rise and patents fall, Health Canada may need to reassess the issue and consider substitutabil-

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367. *See* Prescription Drugs—Generic vs Brand Name, Crossborderpharmacy.com, http://crossborderpharmacy.com/canadian-generics-vs-brand-name.html (last visited Apr. 17, 2010).

368. Health Can., *Draft Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs)* (March 27, 2009), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/consultation/2009-03-seb-pbu-notice-avis-eng.pdf [hereinafter Health Can., *Draft Guidance for Sponsors*].

369. *See id.* at a–b.

370. *See id.* at 2.

371. *Id.* at 4–6.

372. *Id.* at 4.

373. *See* Health Can., *Draft Guidance for Sponsors*, *supra* note 368, at 4.

374. *Id.* at 1.

> [A] suitable reference biologic drug exists that: a) was originally authorized for sale based on a complete data package; and b) has significant safety and efficacy data accumulated such that the demonstration of similarity will bring into relevance a substantial body of reliable data; the product can be well characterized by a set of modern analytical methods; and the biologic drug, through extensive characterization and analysis, can be judged similar to the reference biologic drug by meeting an appropriate set of pre-determined criteria. Products employing clearly different approaches to manufacture than the reference biologic drug (for example, use of transgenic organisms versus cell culture) will not be eligible for authorization as SEBs.

Id.

375. *Id.* at 3, 6. This is made upon request of the Minister and "must include sufficient information to explicitly explain the link." *Id.* at 6.

ity at the pharmacy level, the possibility of a reduced review time for the agency and incentives for manufacturers to produce and market these products. The first drug approved under the subsequent entry biologic review system was Omnitrope® on April 20, 2009.[376]

The European Regulatory Union maintains the benchmark regulation for biosimilar review and approval in the world.[377] This pathway was established in June 2003 through modification of the EU's medical products statutes.[378] The European Agency for the Evaluation of Medicinal Products (EMEA), the European equivalent to the FDA, oversees the implementation of the review process. The regulations approach generic biologics as distinct from traditional generic drugs based on complexity, thus requiring a different approach to an abbreviated approval.[379] Review and approval occurs on a case-by-case basis using product specific guidance documents issued through an open and public process.[380] The system calls for "[a]n appropriate comparability exercise . . . to demonstrate . . . similar profiles in terms of quality, safety, and efficacy."[381] Although the system can approve a biosimilar drug, it leaves the determination of substitution to national authorities.[382] France and Spain recently enacted legislation that prohibits automatic substitution of a generic biologic, and the system as a whole is still in its infancy.[383]

Under EMEA review, a biosimilar application contains non-clinical data, as well as clinical data.[384] The section on non-clinical data is meant to identify changes in response between the two products and is based on in vitro studies, toxicokinetic measurements, etc.[385] The clinical section is in-

376. Notice of Decision for Omnitrope, Health Canada 1 (May 15, 2009), *available at* http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/nd_ad_2009_omnitrope_113380-eng.pdf.

377. *See* Filiz Hincal, *An Introduction to Safety Issues in Biosimilars/Follow-On Biopharmaceuticals*, 7 J. MED., CHEMICAL, BIOLOGICAL, & RADIOLOGICAL DEF. 1, 4 (2009). Interestingly, in 1986 the European Union initially approved a system to approve generic biologics. Gottlieb, *supra* note 214, at S6. This system was quickly seen as incomplete and problematic and abandoned. *Id.*

378. *See* EUROPEAN MEDS. AGENCY (EMEA), COMM. FOR MEDICINAL PRODS. FOR HUMAN USE, GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY-DERIVED PROTEINS AS ACTIVE SUBSTANCE: NON-CLINICAL AND CLINICAL ISSUES 3–4 (Feb. 22, 2006) *available at* http://www.ema.europa.eu/pdfs/human/biosimilar/4283205en.pdf [hereinafter EMEA 2006].

379. *See* Gottlieb, *supra* note 214, at S3, S7.

380. *Id.* at S7.

381. EMEA 2006, *supra* note 378, at 3.

382. Nuala Moran, *Fractured European Market Undermines Biosimilar Launches*, 26 NATURE BIOTECHNOLOGY 5, 5 (2008).

383. *Id.*

384. *See* EMEA 2006, *supra* note 378, at 4–6.

385. *Id.* at 4.

tended to demonstrate clinical comparability, including efficacy and safety.[386] The EMEA guidelines also require a full chemistry evaluation.[387] Guidance documents suggest that comparability efficacy studies may be needed, although they are not required.[388] The extent of abbreviation varies and some approvals will be akin to the brand drug's approval with rigorous data requirements.[389] Additionally, class-specific guidelines can be established for product reviews.[390] The EMEA system provides for an exclusivity period of ten years for an innovator reference product.[391] Moreover, the applicant can obtain another year of exclusivity, for a total period of eleven years, if the biologic gains a new indication in the first eight years of its exclusivity which provides a "significant clinical benefit in comparison [to] existing therapies."[392] The regulations also require post-approval surveillance to monitor such things such as immunogenicity.[393]

The first drug approved under the biosimilar review process in Europe was Omnitrope® in January 2006.[394] In 2007, the world's bestselling biologic, erythropoietin, saw the approval of two biosimilar drugs in Europe, although market penetration has been slow to transpire.[395] The true impact of biosimilars in practice has not yet come to fruition and in many ways the system is still in its early infancy. Advances in technology, experience, and legislation will refine the system over time.

C. *Proposed U.S. Legislation*

In the United States, the FDA approves drug products for marketing under authority of the FDCA and the Public Health Services Act.[396] It has been "argued that the FDA has the authority to approve generic" biologics under

386. *Id.* at 5–6.
387. *See id.* at 5.
388. *See, e.g., id.* at 5–6.
389. *See* Frank, *supra* note 98, at 843.
390. *See* EMEA 2006, *supra* note 378, at 4.
391. EUROPEAN COMM'N, ENTER. & INDUS. DIRECTORATE-GEN., GUIDANCE ON ELEMENTS REQUIRED TO SUPPORT THE SIGNIFICANT CLINICAL BENEFIT IN COMPARISON WITH EXISTING THERAPIES OF A NEW THERAPEUTIC INDICATION IN ORDER TO BENEFIT FROM AN EXTENDED (11-YEAR) MARKETING PROTECTION PERIOD 1 (2007), *available at* http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/guideline_14-11-2007.pdf.
392. *Id.* (internal quotations omitted).
393. *See* EMEA 2006, *supra* note 378, at 6–7.
394. Press Release, EUROPA, Biotech Medicines: First Biosimilar Drug on EU Market (Apr. 20, 2006), http://europa.eu/rapid/pressReleasesAction.do?reference=IP/06/511.
395. Moran, *supra* note 382, at 5.
396. *See* Underwood, *supra* note 228, at 432–33.

an abbreviated follow-on pathway using the current regulatory framework.[397] Nevertheless, the FDA has taken no action on the issue and has left the issue to Congress to legislate.[398]

Over the last few years, there have been a number of proposed, and defeated, bills dealing specifically with generic biologics in the United States.[399] It was not until the push for a national healthcare reform bill gained momentum did the prospect of legislation authorizing generic biologics become increasingly apparent and the chance of success elucidate. Despite strong opposition and quarrel, Congress maintained a steadfast move toward approval of a healthcare bill under the unwavering persistence of President Obama. One measure passed in the Senate[400] and one in the House, thus setting the stage for bicameral national health reform.[401] These two bills each included a provision authorizing generic biologics.

On November 7, 2009, H.R. 3962, the Affordable Health Care for America Act, passed in the House of Representatives by a 220 to 215 vote.[402] Division C, Title V, Subtitle C, Part 2 dealt exclusively with Biosimilars.[403] The bill amended the PHSA and establisheed a framework to approve a generic biologic.[404] A drug was considered "biosimilar" by evidence of analytical studies, animal studies, and clinical data that show no clinically meaningful differences in safety, purity, or potency from the reference (brand) product.[405] It also included a provision, whereby the HHS Secretary can waive the requirement for clinical data; although this matter will need to be further considered either by legislation or regulation.[406] It includes a section

397. *Id.* at 442.

398. *See id.* at 425–26.

399. *See, e.g.*, Access to Life-Saving Medicine Act, H.R. 1038, 110th Cong. (2007); Patient Protection and Innovative Biologic Medicines Act of 2007, H.R. 1956, 110th Cong. (2007); Biologics Price Competition and Innovation Act of 2007, S. 1695, 110th Cong. (2007); Pathway for Biosimilars Act, H.R. 5629, 110th Cong. (2008).

400. Patient Protection and Affordable Care Act, H.R. 3590, 111th Cong. (2009) (enacted). This was originally a House bill, but was co-opted by the Senate, as all revenue bills have to start in the House. *Id.*

401. *See generally* Affordable Health Care for America Act, H.R. 3962, 111th Cong. (2009).

402. CNN.com, House Passes Health Care Reform Bill (Nov. 8, 2009), http://www.cnn.com/2009/POLITICS/11/07/health.care/index.html.

403. H.R. 3962, § 2575. Only one republican voted for this bill. *See* Robert Pear, *Senate Passes Health Care Overhaul on Party-Line Vote*, N.Y. TIMES, Dec. 25, 2009, at 1A.

404. H.R. 3962 § 2575.

405. H.R. 3962 §§ 2575(a)(2), (b)(3).

406. H.R. 3962 § 2575(a)(2).

on guidance documents, and empowers the FDA (HHS Secretary) to issue product class-specific guidance in approving biosimilar drugs.[407]

The bill provided for an exclusivity period of twelve years for innovator products.[408] There are no further exclusivity provisions for changes in indications, dosage form, or route of administration, unlike Hatch-Waxman.[409] The bill includes a rather complex process for patent disputes and includes a provision whereby agreements between the brand and generic company relating to manufacture, marketing, or sale of biosimilar products must be reviewed by the Assistant Attorney General and Federal Trade Commission.[410] It provides a mechanism, whereby a generic biologic can be established as substitutable.[411] The first biologic considered "interchangeable" receives a one year exclusivity to incentive filing, like Hatch-Waxman, authorized for traditional drugs.[412] Additionally, the bill provides for an additional six-month exclusivity period for testing in a pediatric population and charges user fees to the manufacturer, like those authorized under PDUFA.[413]

The Senate bill dealing with generic biologics was H.R. 3590, the Patient Protection and Affordable Care Act.[414] On December 24, 2009 this bill passed in the Senate by a vote of sixty in favor, thirty-nine opposed, and one present/not voting.[415] Title VII, Subtitle A was entitled "Biologics Price Competition and Innovation Act of 2009" and was a close reflection of the House bill.[416] It provided a similar framework to approve a generic biologic drug product through the PHSA.[417] Under this act, a biologic is deemed biosimilar to a reference biologic if analytical studies, animal studies, and clini-

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407. *Id.*

408. *Id.*

409. *See* Affordable Health Care for America Act, H.R. 3962, 111th Cong. § 2575 (2009).

410. *See* Affordable Health Care for America Act, H.R. 3962, 111th Cong. § 2575(a)(2).

411. *Id.* (for biologics that are administered more than once the application must demonstrate safety of switching back and forth).

412. *Id.* (interchangeability is established if the two products are biosimilar, expected to provide the same clinical results, and there is no increased risk by alternating between the two products).

413. *Id.*

414. Patient Protection and Affordable Care Act, H.R. 3590, 111th Cong. (2009) (enacted).

415. Pear, *supra* note 403 (Not a single Republican voted in favor of this bill.). "Senator Jim Bunning, Republican of Kentucky, did not vote." *Id.*

416. *See* H.R. 3590, § 7001 (2009).

417. This provision was authored by Senators Kay Hagan (D-N.C.), Mike Enzi (R-Wyo.), Orrin Hatch (R-Utah) and Barbara Mikulski (D-Md.). Press Release, Biotechnology Indus. Org., Provisions in the Senate Health Care Bill Help Patients, Promote Innovation, Encourage Job Growth (Dec. 24, 2009), *available at* http://bio.org/news/pressreleases/newsitem.asp?id=2009_1224_01.

cal data show no clinically meaningful differences in safety, purity, or potency from the reference (brand) product.[418] Also like the House bill, it provided for an exclusivity period of twelve years for the innovator product, granted a one-year marketing exclusivity for the first product deemed interchangeable, and included a six month pediatric exclusivity provision.[419] Importantly, the bill did not consider pay-to-delay agreements like the House bill.[420] Lastly, the bill required a determination on the savings to the federal government be calculated.[421]

D. *Patient Protection and Affordable Care Act and Biologics Price Competition and Innovation Act*

On March 21, 2010, the House of Representatives voted in support of the Senate-approved H.R. 3590 by a vote of 219-212,[422] setting the state for President Obama to sign into law landmark legislation involving healthcare and for the first time authorizing generic biologics in the United States. On March 23, 2010, the Patient Protection and Affordable Care Act became Public Law 111-148.[423]

The Act establishes a user-fee supported pathway for approving generic biologics through the PHSA.[424] The Act includes a section providing for product class-specific guidance documents to facilitate approval, as are utilized in Europe.[425] It also provides a six month pediatric exclusivity provision which is a valuable social incentive.[426] There is no *Orange Book* reliance for sharing of patent information, and instead the law details an information sharing process between the brand and the generic company on intellectual property.[427]

The generic company does not have to certify any of the brand holder patents and there is no automatic thirty-month-stay provision, under the law which effectively closes the problematic loophole of Hatch Waxman. Instead, the law delineates a multi-step process for patent infringement con-

418. H.R. 3590, § 7002(a)(2).
419. H.R. 3590 § 7002(a)(6)(A),(a)(7)(A), (m)(2)(a).
420. H.R. 3590 § 7002(a)(5)(B).
421. H.R. 3590 § 7003(a).
422. *See* Patient Protection and Affordable Care Act, Pub. L. No. 111-148, §§ 7001–03, 124 Stat. 119 (2010). This bill was decided on strong partisan lines with 219 Democrats voting in favor and 34 voting against. All 178 Republicans voted in opposition.
423. *See id.*
424. *See id.* §§ 7001–03.
425. *Id.* § 7002.
426. *Id.*
427. *See* Patient Protection and Affordable Care Act § 7002.

cerns and requires the generic company to notify the brand company 180 days prior to marketing.[428] This preserves the brand company's ability to seek a preliminary injunction.

The exclusivity period is twelve years from the date of brand drug approval.[429] The debate on this issue was one of the most polarizing. BIO had sought fourteen years.[430] Generic trade associations sought eight years.[431] The White House and President Obama were somewhere in between, seeking exclusivity of ten years.[432] Clearly a significant exclusivity period is a requisite requirement. This issue has been a vital component to the widespread success of the generic industry. Generic drugs often become available the same day the FDA exclusivity period ends on the brand drug and the wide spawn of generics has been notable. As the future of medicine is going to be biologically based, pioneering companies must be confident in the ability to recoup research, development costs, and make a significant profit on their discoveries. However, based on the FTC report and the success of Hatch-Waxman, twelve years seems overly generous and may in fact stifle competition.[433]

The Law provides a one-year exclusivity for the first interchangeable product, which is greater than 180 days authorized under Hatch-Waxman.[434] This provision should help incentivize development and provide reward for generic manufacturers. Nevertheless, the Law failed to bar the use of authorized generics by brand companies to undermine generic development. The law also failed to prohibit pay-to-delay agreements. This has been a conten-

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428. *Id.*

429. *Id.*

430. BIOTECHNOLOGY INDUS. ASS'N, A FOLLOW-ON BIOLOGICS REGIME WITHOUT STRONG DATA EXCLUSIVITY WILL STIFLE THE DEVELOPMENT OF NEW MEDICINES 5 (Sept. 26, 2007), *available at* http://www.bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf 5 (last visited Apr. 2, 2010). BIO cites empirical evidence that the breakeven point for a biologic takes thirteen to sixteen years. *Id.* at 4.

431. *See* Gottlieb, *supra* note 214, at S7. Congressman Waxman, the House Energy and Commerce Chairman, has reportedly sought exclusivity of five to seven years. Jessica Dye, *Obama Wants to Limit Biologic Protection in Health Bill*, LAW360, Jan. 15, 2010, http://www.law360.com/articles/143763.

432. *Id.*

433. *See* Press Release, GPhA Asks President Obama to Urge Congress to Strike Biogenerics from Health Care Reform If Provisions Are Not Substantially Altered, http://www.gphaonline.org/media/press-releases/2009/gpha-asks-president-obama-urge-congress-strike-biogenerics-health-care-ref (last visited Mar. 30, 2010). Generic Pharmaceutical Association strongly opposed this exclusivity period, calling the period "little more than camouflaged protection of the unacceptable and unsustainable status quo." *Id.*

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

tious issue for the industry and the courts, and Congress missed a ripe opportunity to voice its concern.

VII. CONCLUSIONS

In Francisco's Money Speech, as Ayn Rand wrote in *Atlas Shrugged*, "[w]ealth is the product of man's capacity to think."[435] We are at the dawn of landmark legislation geared to modernize the generic pharmaceutical industry and spawn the next era of lower cost medications. A properly structured abbreviated pathway will enhance existing research and discovery, award generic companies the opportunity to compete and decrease the financial burden on the U.S. healthcare system. Clearly, there is a need for generic biologic legislation in the United States and the time has finally arrived. The marketplace for biologics continues to expand, the price for prescription drugs continues to surge, patents for existing products have begun to expire, and analytical technology has reached a sufficient juncture. All the key players are at the table and our elected officials accomplished the task. Now the pressure is on the FDA to deal with the next set of challenges the law will provide.

Undoubtedly, the FDA faces an enormous challenge with the passage of an abbreviated pathway for biologics. As always, the FDA must assure that patient safety trumps all. The FDA can then establish some equivalency system to support product substitution, like the current system whereby some products are substitutable, and others are not.[436] Then, stakeholders such as managed care organizations and pharmacy benefit managers can establish protocols and clinical guidelines to drive practice and decrease costs.[437]

Once generic biologics become available, the market influence and penetration will be unique compared to the current system of traditional generics. Early competition will likely resemble brand-to-brand competition and prices may not be as low as some may anticipate.[438] The four dollar co-pay

435. AYN RAND, ATLAS SHRUGGED 381 (Signet 1996) (1957).

436. Individual states, regulating the practice of pharmacy, may establish a negative drug formulary whereby pharmacists will have a list of drugs that, by law, they cannot substitute, although the FDA finds them interchangeable. *See* FLA. ADMIN. CODE ANN. r. 64B16-27.500 (2010) (Florida's example of a negative drug formulary). This is a public policy issue where a Board of Pharmacy has made a determination in opposition to the FDA. *See id.*

437. *See id.*

438. FTC 2009 REPORT, *supra* note 184, at iii; *see also Emerging Health Care Issues: Follow-on Biologic Drug Competition: Hearing Before the H. Subcomm. on Health Comm. on Energy and Commerce*, 111th Cong. 9 (2009)

may be some time off.[439] Additionally, in vast contrast to traditional generics, some early generic biologic companies may have to utilize unprecedented marketing campaigns to try and drive market share.[440] Ultimately the market acceptance to generic biologics will be similar to traditional drugs over time and patients will see a significant increase in cost savings. Moreover, because the U.S. Government is the largest payor of prescription drugs in this country, government acceptance of these products will have a profound effect on market acceptance.[441]

The likely players to emerge from the generic biologic marketplace are biotechnology companies, big pharmaceutical companies,[442] and large generic houses.[443] Currently, it is traditional generic companies being the most aggressive in developing biologics, especially those with a strong European influence.[444] Generic companies in India will also emerge as early players, especially as that country is slow to respect U.S. patent law.[445] Some claim that the approval of a generic biological approval pathway will deter venture capitalism.[446] This is short sighted. The generic industry in this country has blossomed since Hatch-Waxman and competition only works to make a system more efficient and robust.

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439. *See* Milt Freudenheim, *Side Effects at the Pharmacy*, N.Y. TIMES, Nov. 30, 2006, at C1 (describing Wal-Mart's four dollar generic program and how it prompted its competition like Target to also institute such a program).

440. *See* Moran, *supra* note 382, at 5.

441. *Prescription Drugs: Overview of Approaches to Control Prescription Drug Spending in Federal Programs: Hearing Before the Subcomm. On Federal Workforce, Postal Service, and the District of Columbia of the H. Comm. On Oversight and Government Reform*, 111th Cong. 2 (2009) (Statement of John E. Dicken, Dir., Health Care, Gov't Accountability Office). The Federal Employees Health Benefits Program is the largest employer-sponsored health insurance program in the country covering about eight million federal employees, retirees, and their dependents. *Id.* This includes Medicare, VA, DOD, and Medicaid. *Id.* at 1–3.

442. Merck, one of the largest pharmaceutical companies in the world, recently purchased an entire platform of generic biologic-related assets from Insmed Inc., a smaller biotechnology company, for $130 million. *Insmed Completes Sale of Follow-On Biologics Platform to Merck & Co., Inc. for Gross Proceeds of $130 Million.*, PR NEWSWIRE, (Mar. 31, 2009), http://investor.insmed.com/releasedetail.cfm?ReleaseID=374512.

443. Behnke et al., *supra* note 9, at 2.

444. *Id.*

445. Geeta Anand, *Drug Makers Decry Indian Patent Law*, WALL ST. J. (ONLINE), Feb. 11, 2010, http://online.wsj.com/article/SB10001424052748703455804575057621354459804.html.

446. DON WARE & NICK LITTLEFIELD, FOLLOW-ON BIOLOGICS AND PATENT REFORM: WILL THEY DISCOURAGE VENTURE CAPITAL INVESTMENT IN THE BIOTECHNOLOGY INDUSTRY? 5 (2009), *available at* http://www.foleyhoag.com/NewsCenter/Publications/eBooks/~/media/F4A4DDA1411B44CDB7DC87436809E310.ashx.

The passage of the BPCIA is essential to the future of healthcare and cost containment in the United States. Expectedly, any legislation of this complexity will open unanticipated loopholes. No system is perfect and the law may need further revision and amendments over time. Nevertheless, the future of medicine is upon us and the need for generic biologics is overdue. Science continues to blaze its path, while the corresponding policy inevitably lags. Meanwhile, we are only at the tip of the iceberg. Biobetters[447] and tailored gene therapy[448] are evolving and will pose additional generic considerations that will have to be dealt with. Remember, "[t]his shit's chess, [it ain't] checkers."[449]

447. Biobetters refer to new versions of existing brand drugs with enhanced characteristics such as improved delivery, safety, or efficacy. Behnke et al., *supra* note 9, at 2. Frequently, a basic manipulation of a single amino acid sequence or other biochemical change in an existing drug can provide an improved profile. *See id.*

448. *See generally* W. Kalow, *Pharmacogenetics and Pharmacogenomics: Origin, Status, and the Hope for Personalized Medicine*, 6 PHARMACOGENOMICS J. 162 (2006).

449. TRAINING DAY, *supra* note 1.