IP Theory\_Draft 1 of Class Paper

## Draft 1: Accessing Next-generation Therapeutics in the Developing World: The Perils of Patent Protection, Approval, and the Achievement of Interchangeability for Follow-on Biosimilars

As with property, developing countries need some way of deciding who will receive access to drugs. Affordable generic drugs are desperately needed in many developing countries, yet frequently experience delayed market entry due to "evergreening" tactics employed by large pharmaceutical companies. A recent decision of the Indian Supreme *Court suggests that India is willing to address this issue by reformulating international* patent practice. The April, 2013 decision paves the way for a more stringent application of the "obviousness" patentability standard, a move that will combat efforts by large pharmaceutical companies to delay entry of generic drugs to market. While developing counties like India are increasingly treating access to generic drugs as a national issue, recent domestic legislation also enhances the role played by the United States Patent Office and Congress in supporting the generic drugs industry. One such piece of legislation is the Biologic Price Competition and Innovation Act (BPCIA). Congress enacted the BPCIA in 2010 in an effort to ameliorate the high expense and risk involved with bringing biological therapeutics to both domestic and international markets. Modeled after the Hatch-Waxman Act (HWA), the BPCIA was crafted to protect innovation of new biologics by offering a period of regulatory exclusivity while providing a novel regulatory pathway for approval of generic biologics. However, pioneer and generic manufacturers in the biologics space have faced unique regulatory and patent litigation difficulties relative to their small-molecule drug manufacturer counterparts. This article proposes that the "interchangeability" criteria created by the BPCIA must be modified to account for these differences if the Act is to carry out its purpose of bringing affordable drugs to patients in need throughout the world. In addition, the article will argue for the promotion of more competition between generic companies in order to combat the practice of "Evergreening" carried out by Novartis and other powerful pharmaceutical companies in developing countries.

#### Introduction

There is perhaps no better forum to consider what certain patent laws *should be* than India, a country currently developing a regulatory system to enforce newly-formed patent protections. This article argues that developing countries in desperate need of affordable generic therapeutics should continue to craft patentability criteria in a manner that enhances domestic access to generic drugs. Developing countries like India may, for example, attempt combat "evergreening" tactics employed by large pharmaceutical companies by employing a heightened obviousness criteria for patentability. By exercising a heightened standard relative to Europe and the United States, developing countries may particularly benefit from the dissemination of generic biologic compounds, which represent the forefront of modern medicine yet are excluded from many international markets due to the "evergreening" practices of large pharmaceutical companies.

Biologic compounds remain one of the few sources of relief available to individuals suffering from diseases like HIV and Malaria in the developing world. Malaria alone causes greater than 300 million clinical cases and 1 million deaths annually, accounting for a loss of 1% of gross domestic product (GDP) in Africa.<sup>1</sup> Yet, frequently public and private efforts to develop vaccines for malaria and other critical diseases have faced resistance from large pharmaceutical companies. As a result, companies developing medicines for patients throughout the world experience a delayed entry to market. Perhaps most disturbingly, generic manufacturers capable of delivering the most reasonably priced medicines have been targeted by large pharmaceutical companies such as Roche who wish to unreasonably extending their limited patent monopolies.

<sup>&</sup>lt;sup>1</sup> Thomas C. Luke, *Rationale and plans for developing a non-replicating, metabolically active, radiation-attenuated Pasmodiaum falciparum sporozite vaccine* The Journal of Experimental Biology (2003).

The practices of large corporations focused on delaying generic entry to market have been collectively termed, "Evergreening." In addition, large pharmaceutical companies have engaged in a "reverse payment" schemes, whereby generic developers agree to delay entry to market in exchange for payment.

# I. Corporate "Evergreening" impedes flow of generic biologic compounds to developing countries

Therapeutics under patent protection often prove prohibitively expensive for developing nations like Africa, for whom the price of biologic compounds can mean the difference between widespread hardship and resolution of simple ailments. Since the enactment of the Patent Act in 1952, governing representatives of the both "Western" and BRICS countries have recognized this issue, advocating for an abbreviated pathway for generic drugs and regulatory mechanisms to combat the practice of "Evergreening" by pharmaceutical companies. These movements have been codified into law in several instances. The Doha Declaration established an important mechanism by which participating countries may enforce compulsory licenses for certain classes of medications. In addition, the TRIPS agreement granted participating countries flexibility with respect to how they determine whether patents on "new uses of known compounds" are enforceable.

However, many argue that intellectual property-related United Nations organs including the World Intellectual Property Organization (WIPO) and the United Nations Conference on Trade and Development (UNCTAD) have largely failed in dispensing sufficient attention to generic drug access policy, specifically among developing countries. This failure is typified by provisions of the TRIPS agreement, which merely consist of a flat intellectual property "one-size-fits-all" policy for all WTO-members. In so doing it implicitly corresponded with an earlier World Bank-led neoclassical economic growth approach, wherein the preventable suffering and death of thousands of patients throughout Africa, India and Brazil is viewed as a necessary component of the world innovation incentive architecture. Motivating this homogenous approach to disparate world systems is the view that, in the absence of barriers to market processes, poor economies will be incentivized to "catch up" with richer countries, and will at that time rightly benefit from westernized medicines under patent protection. In response to the practical shortcomings of this view, many countries like India have increasingly treated patent protection as a national issue, crafting legislation to protect their vulnerable local markets.

To put the debate regarding international access to drugs in a modern context, we consider a recent decision by the Delhi Supreme Court in *Novartis v. India*. This case exemplifies a modern trend of developing governments to treat the issue of access to drugs as a national issue, crafting legislation to serve the needs of their largely poor constituents. At issue before the Supreme Court was the meaning of "efficacy" under amendment 3(d) of the Indian Patent Act as applied to a Novartis patent protecting the leukemia drug Gleevec. Novartis had successfully acquired patent protection for the new variation in 30 countries, but many speculated that a similar outcome in India would stem the flow of generic drugs to Africa and other developing nations. Indeed, India is known to supply over 80% of generic HIV drugs to Africa, and curtailing the ability of pharmaceutical companies to extend patent monopoly power

is widely viewed in India as a vital national imperative. In line with this national sentiment, the Delhi Supreme court issued a decision against Novartis in April 2013, narrowly interpreting the term "efficacy" under the Indian Patent Act in a manner that prevents Novartis and other companies from filing patents on entire families of similar compounds.

Despite the reaction of international judicial systems to issues of generic drug access, large pharmaceutical companies have continued to successfully stifle entry of many generic developers to market via two primary strategies (both of which fall under the penumbra of "Evergreening"). The first, as suggested in the preceding paragraph, involves the successful patenting of small variations on known therapeutic compounds. When a company is awarded a patent for a slight variation of a known compound, generic developers of the original compound will face difficulty avoiding infringement liability during the *second* monopoly term. Because the cost of litigation is often substantial (hundreds of millions of dollars on average), small generic companies are frequently forced to settle these rather than challenge the merits of the patent in court.

The second technique employed by pharmaceutical corporations involves the agreement of generic companies to delay their own entry to market in exchange for a "reverse payment" from their pharmaceutical competitor. While these agreements are carefully crafted to serve as attractive and risk-averse investments for growing companies, there are significant international public policy concerns with *further* delaying entry to market of biologic products that have already benefitted from 20 years of patent exclusivity. This article offers an introduction to the mutli-pronged problem of patent monopoly term extension, and analyzes a recent *domestic*  enactment termed the Biologics Price and Competition Act (BPCIA) which attempts to address these concerns by providing an abbreviated pathway for biologic generic drug approval.

This work approaches the issue of access to generic biologic drugs through the exclusive lens of the BPCIA. While several other modern statutes like the America Invents Act raise important additional considerations, the purpose of this work is to specifically analyze the success or failure of the BPCIA towards the achievement of it's central goal: reducing the risk of generic drug development by providing an abbreviated pathway to approval for these modern medicines. This analysis necessitates a detailed consideration of the technology at issue, as modest differences in preparation and purification of these process greatly affect the ability of small generic companies to achieve the critical standard of "interchangeability" necessitated by the BPCIA, and it's predecessor, the Hatch-Waxman Act.

#### A) Biologics, the BPCIA, and the Impending Patent Cliff

Biologics are a class of therapeutics derived from living systems, including bacteria, viruses and mammals.<sup>2</sup> Over the past decade, innovative new approaches to biologic drug repackaging, high-throughput biochemistry and large-scale generation of community resource data has set off an explosion of research within this promising class of medicine<sup>3</sup>. This work will evaluate the statutory framework of the Biologic Price Competition and Innovation Act (referred to here as "BPCIA"), recently enacted in March, 2010, and it's projected impact on internationl

<sup>&</sup>lt;sup>2</sup> Francis S. Collins, *A vision for the future of genomics research: A blueprint for the genomic era*, Nature (2003).

generic investment incentives in this key field. On June 28, 2012, the statute narrowly survived judicial scrutiny when the US Supreme Court upheld the Patient Protection and Affordable Care Act (the "PPACA") in a 5-4 vote.<sup>4</sup> Though passage of the PPACA was pegged as a victory for the Obama administration<sup>5</sup>, several terms affecting "data exclusivity" under the BPCIA remained hotly disputed with regard to generic drug access in the developing world. Critics of the BPCIA question the twelve year data exclusivity term provided for generic biologics developers under the BPCIA, an extension of seven years relative to the HWA provisions.

Some health-advocates view the extended exclusivity term as another lever manipulated by powerful pharmaceutical companies to exact unreasonably high costs for therapies desperately needed in the developing world. However, these "evergreening" practices reflect the real risks involved with biologic drug development, in many cases sustaining biopharmaceutical corporations facing decades-long development pipelines and continued lost of drug revenue. Indeed, annual drugs approved for marketing in the United States has declined from 53 new drugs in 1996 to 39 in 2012.<sup>6</sup> This loss of new drug revenue has failed to counterbalance the loss of sales revenue caused by generic drug competition (853 new generics applications in 2011).<sup>7</sup> In addition, with the recent expiration of more than 70 drug patents, brand-name drug spending has reduced substantially (a decline of \$14.9 billion in 2011 alone). <sup>8</sup> Despite the challenge of

<sup>5</sup> Id.

<sup>&</sup>lt;sup>4</sup> Adam Liptak, *Supreme Court Upholds Health Care Law, 5-4, in Victory for Obama,* New York Times, June 28 (2012).

<sup>&</sup>lt;sup>6</sup> See BURRILL & CO., BIOTECH 2008 LIFE SCIENCES: A 20/20 VISION TO 2030, at 43 (2008); Matthew Arnold, *FDA* BLA Approvals Rose in 2009 While NMEs Stumbled, MED. MARKETING & MEDIA, Dec. 31, 2009

<sup>&</sup>lt;sup>7</sup> See Dave McCleary, *eCTD ANDA Submission Statistics*, CUSTOPHARM BLOG, Oct. 7, 2011, http://www.custopharm.com/blog/bid/73873/eCTD-ANDA-Submission-Statistics.

shrinking revenue and the impending "Patent Cliff" of 2014, investment continues to grow in biopharmaceutical companies with a strong commercial focus capable of generating sustained profits. Indeed, the 12 most commercially successful biological compounds in the United States reached an estimated \$30 billion in value in 2010, and this figure is projected to reach \$129 billion by 2018.<sup>9</sup>

Regardless of the economic and social value of approved biological products, biologic and biopharmaceutical development remains one of the most expensive and risky ventures undertaken by small companies.<sup>10</sup> New conceptual and technological approaches will be needed to match the pace of innovation in this field along with the evolving demands of patients around the world.

The BPCIA represents a modern attempt to balance the need for development incentives on the one hand, and the practical limits of national health care expenditure on the other. Yet, the regulations of the BPCIA have thus far failed to reduce development costs for pioneers, and have also erected new hurdles for generics manufacturers. Generics manufacturers have, for instance, found it difficult to accurately evaluate for the presence of equivalence between protein biosimilars and their expensive brand-name counterparts.<sup>11</sup> This article will demonstrate that these difficulties stem, in large part, from unique aspects of protein, DNA and RNA production, differences which are not properly reflected in the statutory language of the BPCIA and which truly necessitate an extended "data exclusivity" monopoly term.

<sup>&</sup>lt;sup>9</sup> Paula Tironi, *Pharmaceutical Pricing: A Review of Proposals to Improve Access and Affordability of Prescription Drugs*, 19 ANNALS HEALTH L. 311, 328 (2010).

<sup>&</sup>lt;sup>10</sup> See Id.

#### II. Establishing "Similarity" to Reference Biologic Products under the BPCIA

Without a doubt, the technical procedures of the BPCIA which determine equivalency between pioneer and generic biologics have stunted rather than enhanced the flow of life-saving protein biosimilars (generic biologics) to national and international markets.<sup>12</sup> To appreciate the obstacles that traditional protein, DNA and RNA therapeutic developers face under the BPCIA, we must first provide a brief introduction of the drug approval process in the United States.

#### A. <u>The Drug Approval Process</u>

The drug approval process in the United States is unlike any other country. In the U.S., two different statutes control the approval of a new drug: the Federal Food, Drug, and Cosmetic Act (FD&CA) and the Public Health Services Act (PHSA).<sup>13</sup> The sponsor of a novel drug seeking market approval must first complete the pre-clinical and clinical testing required to demonstrate safety and effectiveness under these statutes. The legal requirements for safety and efficacy require "substantial" evidence of efficacy demonstrated through clinical trials. Next, the sponsor must submit a new drug application (NDA) under the FD&CA.<sup>14</sup> The NDA is intended to ensure consistency with respect to efficacy, labeling and methodology in the development of small-molecule drugs. Biologics are approved by submission for a biologics license application

<sup>&</sup>lt;sup>12</sup> *Id.* at 10.

<sup>&</sup>lt;sup>13</sup> David M. Dudzinski, *Reflections on Historical, Scientific, and Legal Issues Relevant to Designing Approval Pathways for Generic Versions of Recombinant Protein-Based Therapeutics and Monoclonal Antibodies*, 60 FOOD & DRUG LJ 143, 221–24 (2005).

<sup>&</sup>lt;sup>14</sup> Peter Barton., FOOD AND DRUG LAW: CASES AND MATERIALS 676–77 (3d ed. 2007) (citing PETER BARTON HUTT, *The Regulation of Drug Products by the United States Food and Drug Administration*, in THE TEXTBOOK OF PHARMACEUTICAL MEDICINE (John P. Griffin & John O'Grady eds., 5th ed. 2006)).

(BLA) under PHSA, in a process that largely mirrors that for small-molecule compounds.<sup>15</sup> While the procedures for reviewing NDAs and BLAs are very similar, the regulatory guidelines for approval of biologics import a somewhat different approval process than their simple smallmolecule counterparts.

### B. The BPCIA, and its expanded period of "data exclusivity"

While the HWA created an abbreviated approval process allowing generics to rely on an originator's clinical trial data,<sup>16</sup> no such provision existed for biologics under the PHS Act. Except for one case to a limited extent, imitators had not been able to rely on an innovator's data —continuous data exclusivity. Thus new market entrants bore the full costly and time-consuming clinical trials in order to attain approval for a biosimilar.<sup>17</sup> Enacted in 2010 as a component of the Patient Protection and Affordable Care Act, the BPCIA implements, among other things, an accelerated approval process biosimilars<sup>18</sup> through an abbreviated drug license application under new Section 351(k).<sup>19</sup> Much debate ensued over the time period of data exclusivity to provide innovators such that they could recoup the enormous R&D expenditures in commercializing a new drug before biosimilars enter the market. A popular Duke study concluded it takes 12.9 to 16.2 years for innovators to break even on new biologics.<sup>20</sup> A study

<sup>&</sup>lt;sup>15</sup>See Id.

<sup>&</sup>lt;sup>16</sup> 21 U.S.C. §355(j) (2006).

<sup>&</sup>lt;sup>17</sup> Johnson, *supra* at 6.

<sup>&</sup>lt;sup>18</sup> See PPACA, Pub. L. No. 111-148 codified as 42 U.S.C.A. §18001 (Mar. 23, 2010) enacting Biologics Price Competition and Innovation Act of 2009 codified as 42 U.S.C.A. §201 (2010).

<sup>&</sup>lt;sup>19</sup> Erika Lietzan, Intellectual Property Owners Association. *The FDA's Guidance on Biosimilars: Understanding the Impact on Patent Prosecution and Litigation.* Webinar. March 22, 2012.

<sup>&</sup>lt;sup>20</sup> Henry Grabowski, *Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 1 NAT. REV. DRUG DISCOV., 479, 486 (2008).

funded by Teva Pharmaceuticals, however, concluded that seven years was sufficient.<sup>21</sup> In its final version, however, the BPCI provides for 12 years of data exclusivity.<sup>22</sup>

The extended period of regulatory exclusivity under the BPCIA has generated substantial post-enactment debate among health-care advocates, especially with reference to generic drug access in developing countries. Some developing countries have responded by writing "anti-evergreening" statutes, curtailing the ability of pharmaceutical companies to secure patents on new uses for known compounds. In a press conference following the April, 2013 decision of the Delhi Supreme Court of India<sup>23</sup> in which patent for a new use of the anti-leukemia drug *Gleevec* was invalidated, Roche announced that it would likely pull drug development out of India entirely.

Some argue that the BPCIA should be amended to include a period of data exclusivity that more closely parallels the benchmarks set by the HWA. However, this article contends that the additional seven years is necessary in light of the significant technical complexities unique to biologic development. A survey of these technical details reveals that, while the period of data exclusivity under the BPCIA is appropriate, other benchmarks established by the Act may have an unexpected chilling effect on the industry. For example, the BPCIA unreasonably raises the bar to achieving "biosimilarity" between pioneer and generic molecules. Under the BPCIA, a reference product must fit a new classification: interchangeability.<sup>24</sup> As this article explains, the

<sup>24</sup> Id.

<sup>&</sup>lt;sup>21</sup> Alexander Brill, Proper Duration of Data Exclusity for Generic Biologics: A Critique 4, 11 (2008).

<sup>&</sup>lt;sup>22</sup> PPACA § 7002(a)(2)(k)(7)(A).

<sup>&</sup>lt;sup>23</sup> Novartis v. Union of India, Delhi Supreme Court, April (2013).

same production and development difficulties that necessitate an extended monopoly term for biologic compounds make achievement of "interchangeability" prohibitively difficult.

#### IV. CONCLUSION

The U.S. Supreme Court recently upheld the Patient Protection and Affordable Care Act, an effort to harmonize with world demand for affordable generic drugs. In doing so, the U.S. Supreme Court decision preserved the BPCIA in a form that many consider inadequate to properly incentivize the development of generic biological therapeutics. At the same time, health-care advocates have bemoaned the extended "data exclusivity" term for biologics under the BPCIA, despite a sharp decline in new drug revenue that has itself reduced the number of pioneer biologics available to the public. Though analogous in part to the Hatch-Waxman Act, several of the BPCIA's provisions fail to insulate developers from the inherent limitations involved with production, further threatening growth of this field. Most importantly, its implementation of a new benchmark of interchangeability for follow-on biologics actually heightens the barrier to the marketing of such medicines.

While amendments to the BPCIA will be required to bring it into full compliance with domestic and international obligations, this article demonstrates that the legislative effort is a step in the right direction. Specifically, it combats "evergreening" practices of large pharmaceutical companies like Novartis, which openly pursue extension of monopoly terms by patenting "new uses for known compounds." This new measure lends the appropriate "data exclusivity" term to biologic developers, while effectively accelerating entry to market of cheap biological therapeutics. By accelerating entry to market of generic drugs in the United States, the BPCIA combats evergreening techniques including the practice of "reverse payments" agreements, which developing countries like India have increasingly combated in an effort to address the growing needs of their large domestic patient populations.