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## Into the Woods: A Biologic Patent Thicket Analysis

Jeffrey Wu

National Chengchi University in Taiwan, [jeffrey.wt.wu@gmail.com](mailto:jeffrey.wt.wu@gmail.com)

Claire Wan-Chiung Cheng

National Chengchi University in Taiwan, [claire.w.cheng@gmail.com](mailto:claire.w.cheng@gmail.com)

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## Into the Woods: A Biologic Patent Thicket Analysis

### Cover Page Footnote

Professor Huang-Chih Sung and Dr. Jiun-I Lai

# INTO THE WOODS: A BIOLOGIC PATENT THICKET ANALYSIS

JEFFREY WU\*

CLAIRE WAN-CHIUNG CHENG\*\*

## ABSTRACT

*Some drug companies, brand biologic companies, in particular, have been accused of covering only a single drug with more than eighty patents. These drug patents accumulate to what critics claim as one of the major culprits of high drug prices—“patent thickets.”*

*This article aims to provide insight into this issue by analyzing the U.S. patents that cover top-selling biologics and small-molecule drugs. Results not only confirm the existence of biologic patent thickets—in which two of the three selected top-selling biologics have accumulated more than forty patents—but also show that more patents cover biologics than small-molecule drugs. Based on more in-depth analysis, this article further argues that the so-called “patent thicket” is, in fact, a cooperative effort of two types of patent thickets—Type I and Type II—that should be distinguished due to their differences in nature and the causes that give rise to them.*

*Defined as large numbers of non-overlapping or inventive patents that cover different aspects of the drug, Type I Patent Thickets are formed due to the complex nature of biologics and biosimilars. Type II Patent Thickets, on the other hand, are arguably overlapping or non-inventive patents that are prone to double patenting. They cover the same aspect of the drug and*

\* MS in Intellectual Property, National Chengchi University in Taiwan. The author gratefully thanks Professor Claire Wan-Chiung Cheng, Professor Huang-Chih Sung, and Dr. Jiun-I Lai for their extremely helpful comments and discussions.

\*\* Corresponding Author (e-mail: [clairex1@nccu.edu.tw](mailto:clairex1@nccu.edu.tw)). Assistant Professor of Law, Graduate Institute of Technology, Innovation, and Intellectual Property Management, National Chengchi University in Taiwan. LLD, Kyushu University (Japan); JSM, Stanford Law School.

*owe their existence to the utilization of terminal disclaimers. The two types of patent thickets jointly contribute to the large number of patents that fend off patent challenges; the stretched year spans of collective patent terms that delay biosimilar entry; and the exorbitant drug prices that harm patients.*

*This article also presents two proposals that may mitigate the negative impacts of patent thickets without completely sacrificing the merits patents themselves provide: one being the election of patents to assert, and the other being the more transformative “All-in-One” approach.*

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## I. INTRODUCTION

Biological products (or biologics) are medicinal products generally derived from living material for the prevention, treatment or cure of human disease.<sup>1</sup> They are highly targeted, efficacious against diseases such as cancer, diabetes, rheumatoid arthritis, and other inflammatory conditions.<sup>2</sup> However, in contrast to chemical compound (or small-molecule) drugs, biologics encounter significantly more challenges than their counterparts due to their larger size and more complex nature.<sup>3</sup> These challenges affect both on the difficulty to manufacture them and most importantly, on the exorbitant prices in the market.<sup>4</sup>

As an effort to increase competition among biologics with the hopes of driving down the high prices of biologics, the U.S. Congress passed the Biologics Price Competition and Innovation Act of 2009 (hereafter “*BPCIA*”)<sup>5</sup> to provide an abbreviated approval pathway for biosimilars (also known as “follow-on biologics”).<sup>6</sup> The purpose of the *BPCIA* is to balance innovation incentives with the promotion of competition and consumer interests by on one hand, allowing biosimilar manufactures to partially reference their clinical trial data to that of an approved biologic’s during the biosimilar approval examination process; and on the other hand, benefiting the innovator with twelve years of data exclusivity and providing an efficient patent dispute resolution process.<sup>7</sup> Nevertheless, biologics are still costly in the U.S. with treatment expenses up to US\$ 25,000 annually per patient for some biologics.<sup>8</sup> Critics argue that these

1. *Frequently Asked Questions About Therapeutic Biological Products*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/> (last visited Mar. 9, 2019).

2. Brian K. Chen et al., *Why Biologics and Biosimilars Remain So Expensive: Despite Two Wins for Biosimilars, the Supreme Court’s Recent Rulings Do Not Solve Fundamental Barriers to Competition*, 78 *DRUGS* 1777, 1777 (2018).

3. JOANNA T. BROUGHER, *INTELLECTUAL PROPERTY AND HEALTH TECHNOLOGIES: BALANCING INNOVATION AND THE PUBLIC’S HEALTH* 161 (2014).

4. *See id.*; Tao Gu et al., *Comparing Biologic Cost Per Treated Patient Across Indications Among Adult US Managed Care Patients: A Retrospective Cohort Study*, 3 *DRUGS - REAL WORLD OUTCOMES* 369, 380 (2016).

5. Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, §§ 7001-7003, 124 Stat. 119, 804-21 (2010) (codified and amended in scattered sections of 42 U.S.C., 35 U.S.C., 28 U.S.C.).

6. Jon Tanaka, “*Shall*” *We Dance? Interpreting the BPCIA’s Patent Provisions*, 31 *BERKELEY TECH. L.J.* 659, 659 (2016).

7. *Id.*

8. *See* Gu et al., *supra* note 4 (for example, in the U.S. 90% of patients with arthritis received etanercept, adalimumab or infliximab and the biologic costs per treated patient in the first year for the above biologics were “US\$24,859 (etanercept), US\$26,537 (adalimumab), and US\$26,468 (infliximab).”).

high prices are partially due to “over-patenting” or “patent thickets” that bar biosimilars from entering the market.<sup>9</sup> However, no literature has thoroughly explored this issue or discussed why this phenomenon is possible. This article attempts to address this gap.

In the next part, this article first provides an overview of biologics and biosimilars, including the differences between biologics and small-molecule drugs; the BPCIA’s efforts to drive down drug prices by increasing competition and introducing biosimilars; and how this effort is not sufficient due to multiple barriers. Part III then demonstrates that one of the barriers is patent thickets by conducting an empirical study on comparing the patents of the top-selling biologics and small-molecule drugs. Part IV carries out an in-depth analysis, arguing that there are *two types* of patent thickets (termed Type I Patent Thickets and Type II Patent Thickets respectively in this article) in the so-called “patent thicket.” As Part V and Part VI explain, while the two types of patent thickets jointly contribute to the complexity of patent litigation and hence the high drug prices, the two types of patent thickets are formed due to different reasons. While the existence of patents in the two types of patent thickets are not wholly without merits, the harmful impacts are real. To balance the interest of multiple stakeholders, Part VII first discusses how current legislative proposals may assist in increasing the transparency of the problem and act as *ex post* regulation. However, it is more desirable to prevent the undesirable impacts beforehand. As such, Part VII also presents two *ex ante* regulation proposals with one being a tweak the USPTO can implement to alleviate the effects of Type II Patent Thickets and the other being a more transformative reform that would target both types of patent thickets collectively without completely sacrificing the benefits patents provide. Part VIII concludes.

9. See, e.g., Danny Hakim, *Humira’s Best-Selling Drug Formula: Start at a High Price. Go Higher*, N. Y. TIMES (Jan. 6, 2018), <https://www.nytimes.com/> (stating that Abbvie Inc.’s aggressive patent strategy has muted competition and contributed to the success of its drug pricing strategy); Peter Loftus & Denise Roland, *By Adding Patents, Drugmaker Keeps Cheaper Humira Copies Out of U.S.*, WALL ST. J. (Oct. 6, 2018), <https://www.wsj.com/>; *Abuse of the Patent System is Keeping Drug Prices High for Patients*, ASS’N FOR ACCESSIBLE MED., <https://accessiblemeds.org/> (last visited Jun. 22, 2019); *Remarks from FDA Commissioner Scott Gottlieb, M.D., as Prepared for Delivery at the Brookings Institution on the Release of the FDA’s Biosimilars Action Plan*, US. FOOD & DRUG ADMIN. (July. 18, 2018), <https://www.fda.gov/>.



## II. BIOLOGICS AND BIOSIMILARS

Before delving into the biologic patent thicket issue, it is imperative to understand what biologics and biosimilars are. Section A first covers the complex nature of biologics and what makes them different from traditional small-molecule drugs. The complicated characteristics of biologics give rise to the challenges in their manufacture and immensely impact, as Section B entails, the development, the cost, and also the booming market thereof. Although the biologic market is prospering, patients are suffering from the high cost of biologics.<sup>10</sup> Section C turns to discuss what biosimilars are and how they and the *BPCIA* are supposed to drive down biologic prices. Unfortunately, current biosimilars face significant barriers to market entry.<sup>11</sup> As Section D presents, these hurdles include scientific and manufacturing challenges; strict regulatory compliances; the presence of patents; and the acceptance of physicians and patients.

### A. What Are Biologics?

Pharmaceutical drugs can be roughly categorized into chemical compound (small-molecule) drugs or biological products (biologics).<sup>12</sup> Small-molecule drugs usually consist of a pure chemical substance, have a well-defined structure, and can be thoroughly characterized.<sup>13</sup> Therefore, once the active ingredient is known, small molecule drugs can be synthesized chemically relatively easily.<sup>14</sup> Biologics, on the other hand, are not so easily defined in structure due to their complex nature.<sup>15</sup> The *BPCIA* defines a biologic as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a

10. See *infra* Part II.B.

11. See *infra* Part II.D.

12. See U.S. FOOD & DRUG ADMIN., *supra* note 1.

13. *Id.*

14. See *id.*

15. *Id.*

disease or condition of human beings.”<sup>16</sup> In simple terms, biologics are large therapeutic protein molecules created by living cells.<sup>17</sup>

A (therapeutic) protein’s structure is fundamentally complicated and is determined during its manufacture and synthesis.<sup>18</sup> Since the unique three-dimensional structure specifies the properties of proteins and is essential to their correct functioning, biologics are primarily dependent on their manufacturing process.<sup>19</sup> Coupled with the fact that biologics are created by living cells—which are very sensitive to alterations in conditions—a slight difference in the manufacturing process, equipment or facilities could result in drastic changes to the final product.<sup>20</sup> These changes could affect the purity, potency, safety, or even the clinical identity of the biologic.<sup>21</sup> Thus, as Hirsch accurately summarizes, for a biologic, “the process is the product, and the product is the process.”<sup>22</sup>

### *B. The Development, the Cost and the Market of Biologics*

Due to the aforementioned complexity of biologics and the need for more diversified resources, biologic manufacturers generally spend a significant amount of expense on research and development.<sup>23</sup> As a reference point, the development cost for the antibody-drug conjugate Brentuximab vedotin<sup>24</sup> was estimated to be US\$ 899.2 million.<sup>25</sup> Besides, manufacturers also spend considerable expenses on complying to the strict

16. 42 U.S.C. § 262(i)(1) (2017).

17. See Dov Hirsch, *The Riddle of the Mysterious Patent Dance Wrapped in an Enigma: Is the Patent Dance of the BPCIA Optional or Mandatory?*, 27 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 645, 650 (2017).

18. See Elysa B. Goldberg, *Fixing a Hole: Will Generic Biologics Find a Niche Within the Hatch-Waxman Act?*, 20 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 327, 333 (2009); U.S. FOOD & DRUG ADMIN., *supra* note 1.

19. See MARY K. CAMPBELL & SHAWN O. FARRELL, *BIOCHEMISTRY*, 84 (7th ed. 2011).

20. U.S. FOOD & DRUG ADMIN., *supra* note 1.

21. Arthur J. Chirino & Anthony Mire-Sluis, *Characterizing Biological Products and Assessing Comparability Following Manufacturing Changes*, 22 NATURE BIOTECH. 1383, 1384 (2004); see U.S. FOOD & DRUG ADMIN., *supra* note 1.

22. Hirsch, *supra* note 17 at 652.

23. See Goldberg, *supra* note 18.

24. Niels W. C.J. van de Donk & Eugen Dhimolea, *Brentuximab Vedotin*, 4 MABS 458, 458, 465 (2012) (explaining that Brentuximab vedotin is “an anti-CD30 antibody conjugated via a protease-cleavable linker to the potent anti-microtubule agent monomethyl auristatin E (MMAE)” and it “offers an important new therapeutic option for patients with heavily pretreated relapsed/refractory Hodgkin lymphoma, systemic ALCL, and primary cutaneous CD30-positive lymphoproliferative disorders.”).

25. Vinay Prasad & Sham Mailankody, *Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval*, 177 JAMA INTERNAL MED. 1569, 1571 (2017).

regulations on the manufacture, approval process, and marketing of biologics.<sup>26</sup>

For a biologic to enter the market, it is required by law to undergo convoluted development approval processes and clinical trials.<sup>27</sup> The process starts with basic research and preclinical studies where scientists search and test for potential biologic candidates in glass tubes, cultured cells and subsequently in live animals.<sup>28</sup> To complicate matters, preclinical studies for biologic candidates require additional protein purification and recipient immune response monitoring.<sup>29</sup> If all goes well in preclinical trials, an Investigational New Drug (IND) application may be submitted to the Food and Drug Administration.<sup>30</sup> The approval of the application allows the biologic candidate to be tested on humans.<sup>31</sup> The biologic candidate then proceeds to undergo three phases of clinical trials where drug safety, efficacy, and regulatory compliance are examined, with each phase having a larger pool of recipients than the preceding phase.<sup>32</sup> If the clinical trials are successful, a Biologics License Application (BLA) may be submitted to the FDA for review; and if the application is approved, the biologic may finally enter the market.<sup>33</sup> The entire development and approval process usually takes up at least twelve years.<sup>34</sup>

However, the daunting development cost and stringent regulations have not scared off pharmaceutical companies.<sup>35</sup> On the contrary,

26. See Hirsch, *supra* note 17, at 656; see, e.g., U.S. FOOD & DRUG ADMIN., *supra* note 1 (“Since there is a significant difference in how biological products are made, the production is monitored by the agency from the early stages to make sure the final product turns out as expected.”).

27. See Richard C. Mohs & Nigel H. Greig, *Drug Discovery and Development: Role of Basic Biological Research*, 3 ALZHEIMER’S & DEMENTIA 651, 656, 656 fig.5 (2017) (for instance, fig 5. presents a general view of the biologic development process).

28. See INST. OF MED. OF THE NAT’L ACAD. COMM. ON ACCELERATING RARE DISEASES RES. AND ORPHAN PROD. DEV. § 1 (Marilyn J. Field & Thomas F. Boat eds., 2010).

29. See *id.* (“The production of sufficient quantities of a biologic for preclinical and clinical development studies requires unique approaches for expression of the proteins and their purification to regulatory standards. . . Second, biologics can potentially elicit an immune response in the recipient. This response must be monitored very closely because it is not always predictable. Thus, biologics may present special issues to be addressed in preclinical studies, such as immunogenicity (i.e., induction of an antibody response) and immunotoxicity (agents intended to stimulate or suppress the immune system may cause cell-mediated changes.)”).

30. *Id.* § 2.

31. See *id.*

32. See *id.* §§ 2-4.

33. See *id.* §§ 4, 5. (Note that the FDA will still constantly review and monitor approved drugs (phase IV) for their safety or efficacy).

34. Mohs & Greig, *supra* note 27, at 651.

35. Emily Waltz, *It’s Official: Biologics Are Pharma’s Darlings*, 32 NATURE BIOTECH. 117, 117 (2014) (“Biologics have replaced small-molecules as the dominant focus of big pharma’s pipeline . . .”).

pharmaceutical companies have shifted their R&D focus from small-molecule drugs onto biologics.<sup>36</sup> Driving forces may include the innovative mechanism of biologics, the ability to raise higher prices, and the diminishing patent lives of small-molecules.<sup>37</sup> In 2018, the U.S. approved a total of 207 new entities (including chemical compounds and biologics) wherein 47% of them were biologics,<sup>38</sup> a substantial increase compared to previous years.<sup>39</sup> Data also show that molecular antibodies (hereinafter mAbs) are gradually dominating, taking up to 53% of all approvals (both biologics and biosimilars) in the U.S. and EU.<sup>40</sup> Currently, mAbs are perhaps the most lucrative single product class, with total sales topping over US\$ 128 billion in 2018.<sup>41</sup> As a matter of fact, the most lucrative biologic is the mAb, Humira<sup>®</sup>.<sup>42</sup> Marketed by Abbvie, Inc., the mega-blockbuster biologic earned US\$ 18 billion in 2017 global sales.<sup>43</sup>

While the market is flourishing, patients are suffering from the astounding high prices of biologic treatments.<sup>44</sup> For instance, the monoclonal antibody biologic against autoimmune disease infliximab costs a patient US\$ 26,468 annually.<sup>45</sup> High biologic prices should not come as a great surprise considering its complex nature, challenging manufacture, and stringent regulations. Nevertheless, for the sake of public interest and affordable healthcare, biologic prices should be reduced. A purportedly effective way to do so is by increasing competition in the biologics market.

36. *Id.*

37. *See id.*

38. *See* Gary Walsh, *Biopharmaceutical Benchmarks 2018*, 36 NATURE BIOTECH. 1136, 1137 (2018).

39. *See id.* (The percentage of genuinely new biologic approvals among new entity approvals in 2010 and 2014 were 21% and 26% respectively).

40. *Id.*

41. *Id.* at 1138.

42. *See* INITIATIVE FOR MED., ACCESS & KNOWLEDGE, OVERPATENTED, OVERPRICED: HOW EXCESSIVE PHARMACEUTICAL PATENTING IS EXTENDING MONOPOLIES AND DRIVING UP DRUG PRICES 3 (2018), <http://www.i-mak.org/>.

43. *Id.*

44. *See* Gu et al., *supra* note 4, at 369 (for example, in the U.S. 90% of patients with arthritis received etanercept, adalimumab or infliximab and the biologic costs per treated patient in the first year for the above biologics were US\$ 24,859 for etanercept; US\$ 26,537 for adalimumab; and US\$ 26,468 for infliximab).

45. *See* Gu et al., *supra* note 4.

### C. Biosimilars and the BPCIA as the Solution to High Biologic Prices

Driving down drug prices with increased competition through expedited approval pathways is not without precedent.<sup>46</sup> In 1984, the U.S. Congress enacted the Drug Price Competition and Patent Restoration Act<sup>47</sup>—also known as the Hatch-Waxman Act—to incentivize lower-cost generic (small-molecule) drugs to enter the market.<sup>48</sup> Under the Act, manufacturers only need to demonstrate that their generic drug candidate is “pharmaceutically equivalent” and “bioequivalent” to an approved drug.<sup>49</sup> The Act thus significantly decreased the time and cost spent on proving the drug’s clinical safety and efficacy; and subsequently lowered the price of drugs.<sup>50</sup>

However, the regulatory structure of the Hatch-Waxman Act is somewhat inapplicable to biologics.<sup>51</sup> For biologics, it is often impossible to demonstrate bioequivalence—an essential requirement under the Hatch-Waxman Act.<sup>52</sup> The difficulty lies in the complex nature and the substantially variable manufacture of biologics.<sup>53</sup> Hence, as a means to address the high biologic prices and to serve as the biologic equivalent pathway of the Hatch-Waxman Act, the U.S. Congress passed the *BPCIA* in 2009. Under the *BPCIA*, approval is based upon “biosimilarity” instead of “bioequivalence.”<sup>54</sup>

#### 1. Biosimilarity and interchangeability

A “biosimilar”—the entity claiming “biosimilarity”—is a biologic product that is “highly similar to the reference product<sup>55</sup> notwithstanding minor differences in clinically inactive components; and [has] no clinically meaningful differences between the biological product and the reference

46. See Alexej Ladonnikov, *The Biosimilar Patent Dance - If You Don't Dance, You're No Friend of Mine*, 35 SANTA CLARA HIGH TECH. L.J. 135, 138 (2018); see Cindy Navarro, *It Takes Two to Tango: The BPCIA's Mandatory Patent Dance*, 45 AIPLA Q.J. 291, 298 (2017).

47. Drug Price Competition and Patent Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended in scattered sections of 21 U.S.C., 35 U.S.C. and 42 U.S.C.).

48. Margo A. Bagley, *Patent Term Restoration and Non-Patent Exclusivity in the US*, in PHARMACEUTICAL INNOVATION, COMPETITION AND PATENT LAW 111, 114 (Josef Drexler & Nari Lee eds., 2013).

49. *Id.*

50. *See id.*

51. Ladonnikov, *supra* note 46, at 139.

52. Bagley, *supra* note 48, at 134.

53. *See id.*

54. 42 U.S.C. § 262(k); see Bagley, *supra* note 48, at 134.

55. *Id.* § 262(i)(4) (explaining a reference product is an approved biologic the biosimilar claims “biosimilarity” to.).

product in terms of the safety, purity, and potency of the product.”<sup>56</sup> To determine “highly similarity” to the reference product, extensive analysis of the structure and function of the reference product and the biosimilar candidate needs to be conducted.<sup>57</sup> The characteristics analyzed include purity, chemical identity, and bioactivity.<sup>58</sup> Minor differences between the biosimilar candidate and the reference product in clinically inactive sites are acceptable but should be closely monitored and evaluated upon examination for approval.<sup>59</sup> Besides proving highly similarity, biosimilar applicants also need to demonstrate that the biosimilar candidate has no clinically meaningful differences between the reference product.<sup>60</sup> This demonstration is generally carried out through human pharmacokinetic (exposure) and pharmacodynamic (response) studies, and clinical immunogenicity assessments.<sup>61</sup>

The *BPCIA* also establishes a pathway where manufacturers can apply for “interchangeability.”<sup>62</sup> An “interchangeable product” is a biosimilar that meets additional requirements where the proposed interchangeable product “can be expected to produce the same clinical result as the reference product in any given patient; and for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.”<sup>63</sup> As an incentive of achieving interchangeability, the *BPCIA* grants the first interchangeable product of each reference product one year of exclusivity.<sup>64</sup> Within such period, the FDA will not approve any subsequent interchangeable product applications referencing the same reference product.<sup>65</sup> However, as of November 2019, no biosimilar has achieved interchangeability status.<sup>66</sup>

56. *Id.* § 262(i)(2).

57. *Biosimilar and Interchangeable Products*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/> (last visited Mar. 18, 2019).

58. *Id.*

59. *Id.*

60. *Id.*

61. *Id.*

62. 42 U.S.C. § 262(k)(4).

63. *Id.* §§ 262(k)(4)(A)(ii), (B).

64. *Id.* § 262(k)(6).

65. *Id.*

66. *See Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/> (last updated Nov. 5, 2019).

By providing a pathway to claim biosimilarity and interchangeability, the *BPCIA* allows biologic applicants having products similar to an approved biologic waive the requirement to individually establish the safety and effectiveness of the proposed products.<sup>67</sup> By doing so, significant drug development time and costs are saved; and patient treatment costs should theoretically be reduced as a consequence.<sup>68</sup> When granting benefits to the biosimilar manufacturers, the *BPCIA* must also consider the interests of the reference product sponsors. The *BPCIA* guarantees twelve years of regulatory exclusivity (wherein the FDA will not approve any biosimilars referencing to that biologic).<sup>69</sup> In fact, the FDA will not even accept any biosimilar applications within the first four years the reference product is approved.<sup>70</sup>

## 2. *BPCIA*'s patent dispute resolution system

Another mechanism established by the *BPCIA* to accelerate biosimilars to market is its patent dispute resolution system,<sup>71</sup> or more colloquially referred to as the “patent dance.”<sup>72</sup> A patent dispute resolution process is crucial under the current *BPCIA* regulatory scheme because unlike the Hatch-Waxman, the *BPCIA* does not demand the publication of a list of patents that cover the approved biologics.<sup>73</sup> The patent dance aims to identify patents that are likely subject to future litigations and to trigger immediate lawsuits in the hopes of resolving the disputes as early as possible.<sup>74</sup> The patent dance is a two-stage process that provides a means

67. See *Biosimilar Development, Review, and Approval*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/> (last visited Mar. 18, 2019) (“[A] manufacturer that shows its proposed biosimilar product is highly similar to and has no clinically meaningful differences from the FDA-approved reference product may rely in part on FDA’s previous determination of safety and effectiveness for the reference product for approval. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products, additional therapeutic options, and reduced costs for patients.”).

68. See *id.*

69. 42 U.S.C. §§ 262(k)(7)(A).

70. *Id.* §§ 262(k)(7)(B).

71. *Id.* § 262(l) (The patent dispute resolution system, or the “patent dance”, refers to the patent disclosure requirement in 42 U.S.C. § 262(l)).

72. Lindsay Kelly, *Biologics in the Practice of Law*, 39 HARV. J.L. & PUB. POL’Y 21, 25 (2016).

73. See Carl J. Minniti III, *Sandoz v. Amgen: Why Current Interpretation of the Biologic Price Competition and Innovation Act of 2009 Is Flawed and Jeopardizes Future Competition*, 97 J. PAT. & TRADEMARK OFF. SOC’Y 172, 178 (2009). But see Biologic Patent Transparency Act, S.659, 116th Cong. (2019) (a bill sponsored by Senators Susan M. Collins and Tim Kaine that requires the disclosure of patents claiming to cover FDA approved biologics in the purple book.); Purple Book Continuity Act of 2019, H.R.1520, 116th Cong. (2019) (a bill that requires the disclosure of patent exchange information); Part VII.B., *infra*.

74. See Minniti III, *supra* note 73, at 178.

for biosimilar applicants and reference product sponsors to exchange information and for the parties themselves to determine the patents for litigation.<sup>75</sup>

The first stage of the patent dance starts, if at all, after the biosimilar applicant (hereinafter, Applicant) submits an abbreviated Biologic License Application (hereinafter, aBLA), creating an artificial infringement.<sup>76</sup> Within 20 days of the submission, the Applicant should (1) *notify the reference product sponsor (hereinafter, RPS) their biosimilar application and provide a copy of the application and relevant manufacturing information to the RPS.*<sup>77</sup> Within 60 days of the reception of (1), the RPS should provide (2) *a list of patents the RPS believes the Applicant's biosimilar will infringe and the patents the RPS is willing to license, if any.*<sup>78</sup> After receiving (2), the Applicant should provide (3) *a list of patents that the Applicant believes its biosimilar has infringed if any; a statement describing, on a claim by claim basis, why all the patents listed by the RPS are not enforceable, invalid, or will not be infringed by the Applicant's biosimilar; or a statement that the Applicant will not market the biosimilar before the expiration of the patents.*<sup>79</sup> Within 60 days of receiving (3), the RPS should provide (4) *a statement in response to (3), explaining the validity, enforceability of the patents and that why the Applicant's biosimilar will infringe the patents.*<sup>80</sup> Upon receipt of (4), the parties should negotiate in good faith on which of the listed patents should be litigated.<sup>81</sup> If there is an agreement, the RPS should file a patent infringement suit on the agreed patents within 30 days.<sup>82</sup> If both parties do not reach an agreement regarding (4) within 15 days, the parties shall exchange (5) *a list of patents that each believes should be litigated.*<sup>83</sup> The number of patents on the RPS's list cannot exceed that of the Applicant's unless the Applicant lists none, in which the RPS should list one.<sup>84</sup> Within 30 days of the list

75. See Minniti III, *supra* note 73 at 179 (“[B]y engaging in *required* exchanges of information regarding patents claimed to cover the reference product, the parties themselves determine the number of patents subject to litigation [emphasis added]”). *But see* Ladonnikov, *supra* note 43, at 145 (stating that the patent dance is not mandatory according to *Sandoz v. Amgen*, 137 S. Ct. 1664, 1668-69 (2017); thus, the patent dance is more of a *provided means* than a requirement.)

76. 35 U.S.C. § 271(e)(2)(C); 42 U.S.C. § 262(l)(2).

77. 42 U.S.C. § 262(l)(2).

78. *Id.* § 262(l)(3)(A).

79. *Id.* § 262(l)(3)(B).

80. *Id.* § 262(l)(3)(C).

81. *Id.* § 262(l)(4)(A).

82. *Id.* § 262(l)(6)(A).

83. *Id.* § 262(l)(5)(B)(i).

84. *Id.* § 262(l)(5)(B)(ii).



exchange, the RPS may file patent infringement suit on any patents listed on (5).<sup>85</sup>

The second phase of the patent dance is triggered when the Applicant notifies the RPS of its intent to market the biosimilar, in which the notification should be 180 days before the date of marketing and regardless of the FDA approval of the biosimilar.<sup>86</sup> After receiving the notice and before the marketing of the biosimilar, the RPS may seek a preliminary injunction of the biosimilar concerning any patents listed on (2), (3) or any newly issued patent that is not litigated.<sup>87</sup>

#### D. Biosimilar Entry Barriers

Unfortunately, despite the efforts of the *BPCIA*, biosimilars are still finding it difficult to reach the market.<sup>88</sup> According to a data analysis conducted by Kaiser Health News, as of January 2019, 57% of the 16,000 small-molecule drugs approved by the FDA since January 2017 are on sale.<sup>89</sup> However, within the same period, only 5 of the 13 approved biosimilars, or roughly 38%, were launched.<sup>90</sup> This rate may indicate that biosimilars are facing significant barriers.<sup>91</sup>

Although the development of biosimilars is relatively less expensive than that of novel biologics, the development cost for biosimilars is still high—with estimations up to US\$ 200 million for complex molecular antibodies.<sup>92</sup> The high costs can be explained by referring to the previously discussed complex nature of biologics—a minor difference in manufacture may result in a dramatically different outcome.<sup>93</sup> Coupled with the fact that many trade secrets protect manufacturing processes, biosimilar manufacturers would have to apply a reverse engineering approach to dissect the manufacturing process, which is both expensive and time-

85. *Id.* § 262(l)(6)(B).

86. *Id.* § 262(l)(8)(A); *Sandoz v. Amgen*, 137 S. Ct. 1664, 1680 (2017) (“[T]he [A]pplicant may provide notice either before or after receiving FDA approval.”).

87. 42 U.S.C. §§ 262(l)(7), (8).

88. See *FDA Approvals*, BIG MOLECULE WATCH, <https://www.bigmoleculewatch.com/> (last updated July 31, 2019) (providing a chart regarding whether the approved biosimilars are launched, in which as of Nov 5, 2019, only 9 of 24 approved biosimilars are launched).

89. See Sydney Lupkin & Jay Hancock, *Trump Administration Salutes Parade of Generic Drug Approvals, But Hundreds Aren't For Sale*, KAISER HEALTH NEWS (Feb. 7, 2019), <https://khn.org/>.

90. See BIG MOLECULE WATCH, *supra* note 88.

91. See ALEX BRILL & CHRISTY ROBINSON, *STEPS TO REDUCING BARRIERS TO BIOSIMILARS IN THE UNITED STATES* 4 (2018), <https://www.boehringer-ingenelheim.us/>.

92. FED. TRADE COMM’N, *EMERGING HEALTH CARE ISSUES: FOLLOW-ON BIOLOGIC DRUG COMPETITION* iii (Jun. 2008), <https://www.ftc.gov/>.

93. U.S. FOOD & DRUG ADMIN., *supra* note 1.

consuming.<sup>94</sup> As outlined previously, manufacturers also need to comply with strict regulations to achieve biosimilar status, which includes the demonstration of “highly similar” and “having no clinically meaningful differences to reference biologics.”<sup>95</sup> These requirements may present barriers as the demonstration of these characteristics may still require expensive clinical trials.<sup>96</sup> Another barrier for biosimilars is physician and patient acceptance.<sup>97</sup> Physicians may either actively think that biosimilars have lower quality than their referenced biologics<sup>98</sup> or exhibit “prescription inertia.”<sup>99</sup> To complicate matters, the lack of information among patients also presents a problem.<sup>100</sup> Finally, patents would also delay the entry of biosimilars and present significant challenges. Notably, if multiple patents are covering the biologic.<sup>101</sup>

### III. EVIDENCE OF BIOLOGIC PATENT THICKETS: AN EMPIRICAL STUDY

A rebuttal may be that these hurdles are not unique to biosimilars. However, small-molecule generic drugs, despite facing similar challenges,<sup>102</sup> have nevertheless, successfully driven down drug prices.<sup>103</sup> For example, Yixin (Iris) Wang et al. showed that the limited efficiency of

94. See Evelien Moorkens et al., *Overcoming Barriers to the Market Access of Biosimilars in the European Union: The Case of Biosimilar Monoclonal Antibodies*, 7 FRONT PHARMACOLOGY 1, 3 (2016).

95. U.S. FOOD & DRUG ADMIN., *supra* note 57.

96. See Steven Kozlowsk, *Developing the Nation’s Biosimilars Program*, 365 NEW ENG. J. OF MED. 385, 387-88 (2011).

97. BRILL & ROBINSON, *supra* note 91, at 8.

98. Judy Crespi-Lofton & Jann B. Skelton, *The Growing Role of Biologics and Biosimilars in the United States: Perspectives from the APhA Biologics and Biosimilars Stakeholder Conference*, 57 J. AM. PHARM. ASSOC. e1, e5 (2017).

99. BRILL & ROBINSON, *supra* note 91, at 8.

100. See BRILL & ROBINSON, *supra* note 91, at 8 (stating that 70% of U.S. respondents in the general population from a recent survey had never heard of biosimilars and 54% of patients have never heard of biosimilars.).

101. INITIATIVE FOR MED., ACCESS & KNOWLEDGE, *supra* note 42.

102. See e.g., Yixin (Iris) Wang et al., *Manufacturing and Regulatory Barriers to Generic Drug Competition: A Structural Model Approach* 33 (Mar. 21, 2018), <http://dx.doi.org/10.2139/ssrn.3145635> (for example, the manufacturing complexity and regulation processing barriers); see William H. Shrank et al., *Physician Perceptions About Generic Drugs*, 45 ANN PHARMACOTHERAPY 31, 34 (2011).

103. See Garth Boehm et al., *Development of the Generic Drug Industry in the US After the Hatch-Waxman Act of 1984*, 3 ACTA PHARM. SINICA B 297, 309 (2013); see also Atanu Saha et al., *Generic Competition in the US Pharmaceutical Industry*, 13 INT’L J. ECON. BUS. 15, 35 (2006) (stating that “results show that brand prices do react to generic competition; each additional entrant is associated with a 0.2% average decline in brand prices”); *Generic Competition and Drug Prices*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/> (last updated: Nov. 20, 2017).

the generic approval pathway might impair market competition;<sup>104</sup> and Shrank et al. demonstrated that although the majority of selected U.S. physicians are comfortable with the prescription and efficacy of generics, there still consists of a meaningful proportion of physicians that are concerned about the quality of generics.<sup>105</sup> However, as this Part demonstrates, biosimilar manufacturers face more patents in contrast to small-molecule generics. These patents, or “patent thickets,” has, in turn, resulted in a lower launch to approval ratio for biosimilars compared to small-molecule drugs.<sup>106</sup> Without biosimilar competition in the market, brand name biologics would have the luxury to raise drug prices at will.<sup>107</sup>

To demonstrate the so-called “patent thickets” biosimilar manufacturers encounter, this Part conducts an empirical study regarding the patents that cover the top-selling biologics and small-molecule drugs in the U.S.. Section A first covers what a patent thicket is while Section B discusses the recent criticism against biologic patent thickets. Next, Section C presents the research method of the empirical study, including how the top-selling drugs in the U.S. were selected; how the patents of these drugs were retrieved and filtered; and how these results are presented in Section D. Before dissecting patent thickets, Section E conducts a preliminary analysis on the patent counts of these selected drugs.

#### A. What Is a Patent Thicket?

A patent thicket is “a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology;”<sup>108</sup> or more simply put: “multiple patents that cover a single product or technology.”<sup>109</sup> The term probably first came up in the 1970s<sup>110</sup> regarding an antitrust lawsuit against Xerox, in which the plaintiff, SCM Corporation, claims that Xerox had “created a ‘patent thicket’ strong enough to prevent SCM and others from making plain-paper

104. Wang et al., *supra* note 102

105. Shrank et al., *supra* note 102, at 36.

106. See BIG MOLECULE WATCH, *supra* note 88.

107. See Hakim, *supra* note 9.

108. Carl Shapiro, *Navigating the Patent Thicket: Cross Licenses, Patent Pools, and Standard Setting*, in 1 INNOVATION POL’Y AND THE ECO. 119, 120 (Adam B. Jaffe et al. eds., 2001), <https://www.nber.org/chapters/c10778.pdf>.

109. Ian Ayres & Gideon Parchomovsky, *Tradable Patent Rights*, 60 STAN. L. REV. 863, 864 (2007).

110. See Ayres & Parchomovsky, *supra* note 109, at 894 n.5.

office copiers.”<sup>111</sup> Some literature has also added that a patent thicket exists when the owners of these overlapping rights belong to more than one entity.<sup>112</sup> However, for the sake of discussing biologic patent thickets, this article does not add this premise to the patent thicket definition. This decision is because the purpose of this article is to discuss the “formidable wall of patents” established by the reference product sponsor (or the brand biologic company), which is a single entity (or its subdivisions) rather than different entities.

When discussing biologic patent thickets, the concept of “evergreening” must also be introduced. When drug companies evergreen, they “extend the market exclusivity of a drug beyond the life of its original patent by obtaining multiple patents that cover different aspects of that drug, including the active ingredient, formulations, methods of manufacturing, chemical intermediates, mechanisms of actions, packaging, screening methods, and biological targets.”<sup>113</sup> Generally, evergreening is more of seeking an economic advantage than searching a more therapeutic advantage.<sup>114</sup> Evergreening is hardly anything new, even for branded small-molecule drug companies.<sup>115</sup>

The difference between patent thickets and patent evergreen is that the concern of the former is the number of patents while that of the latter is the increased year span of the collective patent term. However, it should be stressed that the extents of patent thickets and patent evergreening do interplay with one another, with the former having the inherent capability to achieve the latter.<sup>116</sup>

111. Robert J. Cole, *SCM v. Xerox: Paper Blizzard for \$1.8 Billion*, N.Y. TIMES (Jun. 27, 1997), <https://www.nytimes.com/>.

112. See, e.g., Adam Mossoff, *The Rise and Fall of the First American Patent Thicket: The Sewing Machine War of the 1850s*, 53 ARIZ. L. REV. 165, 166–67 (2011) (“A ‘patent thicket’ exists when too many patents covering individual elements of a commercial product are *separately owned by different entities*.” (emphasis added)); Stu Woolman et al., *Evidence of Patent Thickets in Complex Biopharmaceutical Technologies*, 53 IDEA 1, 2 (2013) (“A patent thicket exists when *two or more parties* have overlapping patent rights and a potential manufacturer must negotiate licenses with each patent owner in order to bring a product to market without infringing on the rights of the patentees.” (emphasis added)).

113. Jodie Liu, *Compulsory Licensing and Anti-Evergreening: Interpreting the TRIPS Flexibilities in Sections 84 and 3(d) of the Indian Patents Act*, 56 HARV. INT’L L.J. 207, 220 (2015).

114. Roger Collier, *Drug Patents: The Evergreening Problem*, 185 CMAJ e385, e385 (2013).

115. See Robin Feldman, *May Your Drug Price Be Evergreen*, UC HASTINGS RES. PAPER no. 256, 49 (October 29, 2017), <https://ssrn.com/abstract=3061567> (showing that “40% of all [small-molecule] drugs available on the market created additional market barriers by adding patents or exclusivities.”).

116. See *infra* Part V.B.

### B. Biologic Patent Thickets

In its answer and counterclaims against AbbVie, Inc. (hereinafter, “*AbbVie*”), Boehringer Ingelheim International GmbH, Boehringer Ingelheim Pharmaceuticals, Inc., and Boehringer Ingelheim Fremont, Inc. (hereinafter, *Boehringer Ingelheim*) accused *AbbVie* of deliberately forming a “patent thicket” to block out competitors.<sup>117</sup> *Boehringer Ingelheim* explicitly stated that,

“all 74 patents listed in paragraphs 57-58 of [AbbVie’s] complaint<sup>118</sup>, which Plaintiffs identified as the then-existing patents for which a claim of patent infringement could reasonably be asserted with respect to the BLA Product, were issued between 2012 and 2017 . . . stem from less than half as many patent families . . . share common specifications and have overlapping and nearly identical claims. . . Many of Plaintiffs’ patents from different families also have substantially similar disclosures and claims, despite claiming priority to different applications.”<sup>119</sup>

Indeed, in a presentation regarding *AbbVie*’s strategy in 2015, the company has proudly presented its broad U.S. Humira<sup>®</sup>—*AbbVie*’s brand name for adalimumab—“patent estate,” describing 75 patents covering formulations, treatment uses and manufacturing processes of the drug.<sup>120</sup> Furthermore, in 2019, Richard Gonzalez, CEO of *AbbVie*, acknowledged the company’s success on securing 136 patents on Humira<sup>®</sup>.<sup>121</sup>

However, *AbbVie* is not alone. Others have also condemned other biologic manufacturers for similar actions.<sup>122</sup> To further explore this issue

117. REDACTED VERSION of 208 MOTION for Leave to File Amended Answer by Boehringer Ingelheim Fremont, Inc., Boehringer Ingelheim International GMBH, Boehringer Ingelheim Pharmaceuticals, Inc. at 70, *AbbVie Inc. et al v. Boehringer Ingelheim International GMBH et al*, CIVIL No. 17-1065-MSG-RL (D. Del. Sep. 21, 2018) (No. 209) (hereinafter, “*BI’s Motion for Leave to File Amended Answers*”) (“[o]n information and belief, Plaintiffs engaged in a pattern of pursuing numerous overlapping and non-inventive patents for the purpose of developing a “patent thicket,” using the patenting process itself as a means to seek to delay competition against its expensive and lucrative adalimumab product. That strategy has generated, according to paragraph 18 of Plaintiffs’ complaint, more than 100 patents.”).

118. Complaint, *AbbVie Inc. et al v. Boehringer Ingelheim International GMBH et al*, CIVIL No. 17-1065-MSG-RL (D. Del. Aug. 2, 2017) (No. 1) (hereinafter, “*AbbVie v. BI complaint*”).

119. *BI’s Motion for Leave to File Amended Answers* at 70.

120. Richard Gonzalez, *AbbVie Long-Term Strategy* at 14 (2015), <http://www.biotechduediligence.com/>.

121. Joe Cahill, *Taking Aim at Humira’s Patent Fortress*, CRAIN’S CHI. BUS. (Mar. 01, 2019), <https://www.chicagobusiness.com/>.

122. See, e.g., Zachary Silbersher, *Did AbbVie Create a Wrongful “Patent Thicket” Around Humira<sup>®</sup>?*, MARKMAN ADVISORS (Aug. 27, 2018), <https://www.markmanadvisors.com/> (stating that if *Boehringer Ingelheim*’s counterclaims against *AbbVie* works could impact biologics sold by Roche,

and to prove that biologic patent thickets do exist, analysis on granted U.S. patents covering Humira<sup>®</sup>, Enbrel<sup>®</sup>, and Rituxan<sup>®</sup> (known as MabThera<sup>®</sup> outside of the US) —the top-three-selling biologics in the U.S based on 2018 sales revenue—were conducted. Furthermore, to serve as a control group for comparison, patent searches on U.S. granted patents covering Revlimid<sup>®</sup>, Eliquis<sup>®</sup>, and Lyrica<sup>®</sup>—the top-three-selling small-molecule drugs in the U.S. based on 2018 sales revenue—were also carried out. By using the relative amount of core and peripheral patents as criteria to assess the extent of patent thickets show that among the top best-selling drugs in the U.S., biologics tend to form patent thickets compared to small-molecule drugs.<sup>123</sup>

### C. Research Method

#### 1. Top three best-selling biologics and small-molecule drugs in the U.S. based on 2018 sales revenue

In order to identify the top three best-selling biologics and small-molecule drugs based on their 2018 U.S. sales revenues, this study first identified potential candidates based on Nature's report on top drugs and companies by sales in 2018<sup>124</sup> and BioSpace's report on the top 10 best-selling drugs in the U.S. based on sales in 2017.<sup>125</sup> The candidates were categorized into either biologics or small-molecule drugs and ranked according to their U.S. sales in U.S. dollars based on the financial reports of the companies that market the drug. F. Hoffmann-La Roche (hereinafter, *Roche*) was the only company that did not list its financial data in U.S. dollars.<sup>126</sup> The company's U.S. sales revenue statistics were thus converted from Swiss Francs (CHF) into U.S. dollars based on the average exchange rate of 2018.

The top three biologics and small-molecule drugs were selected for patent research and analysis. The selected biologics, their marketing companies and their calculated 2018 U.S. sales revenues are listed in Table

including Avastin<sup>®</sup>, Herceptin<sup>®</sup> and Rituxan<sup>®</sup>, which has also arguably pursued the strategy of fortifying against biosimilars with patent thickets).

123. Three of the top four drugs ranked according to patent counts are biologics. *See infra* Part III.E. The definition of core patents and peripheral patents can be found in Part III.C.4.

124. Lisa Urquhart, *Top Drugs and Companies by Sales in 2018*, 18 NATURE REV. 245, 245 (2019).

125. Mark Terry, *Drum Roll, Please! Top 10 Bestselling Drugs in the U.S.*, BIOSPACE (May 21, 2018), <https://www.biospace.com/>.

126. *See Investor Update*, F. HOFFMANN-LA ROCHE 15 (Jan. 31, 2019), <https://www.roche.com/>.

1 below; and the selected small-molecule drugs and their related information are listed in Table 2 below.

Table 1: Top Three Best-Selling Biologics Based on 2018 U.S. revenue

Ranking	Marketing Company	Brand Drug Name	2018 U.S. Sales (in US dollars)
1	AbbVie	Humira®	13.69 billion <sup>127</sup>
2	Amgen <sup>128</sup>	Enbrel®	4.81 billion <sup>129</sup>
3	Roche/Biogen <sup>130</sup>	Rituxan®	4.39 billion <sup>131</sup>

Table 2: Top Three Best-Selling Small-Molecule Drugs Based on 2018 U.S. Revenue

Ranking	Marketing Company	Brand Drug Name	2018 U.S. Sales (in US dollars)
1	Celgene <sup>132</sup>	Revlimid®	6.47 billion <sup>133</sup>
2	BMS <sup>134</sup> /Pfizer <sup>135</sup>	Eliquis®	5.61 billion <sup>136</sup>
3	Pfizer	Lyrica®	3.69 billion <sup>137</sup>

127. AbbVie Reports Full-Year and Fourth-Quarter 2018 Financial Results, ABBVIE, INC. (Jan. 25, 2019), <https://news.abbvie.com/>.

128. Amgen, Inc. [hereinafter *Amgen*]. Enbrel® is marketed by *Amgen* in the U.S. and by Pfizer Inc. and Takeda Pharmaceutical Company Ltd. outside of U.S. See Eric Palmer, *Enbrel*, FIERCEPHARMA, <https://www.fiercepharma.com/special-report/enbrel> (last visited Jun. 28, 2019).

129. Amgen Reports Fourth Quarter and Full Year 2018 Financial Results, AMGEN, INC. (Jan. 29, 2019), <https://www.amgen.com/media/news-releases/2019/01/amgen-reports-fourth-quarter-and-full-year-2018-financial-results/>.

130 Biogen, Inc. [hereinafter as *Biogen*].

131. Even though *Biogen* co-markets Rituxan® with *Roche*, due to *Biogen* not disclosing its Rituxan® 2018 U.S. revenue, the revenue of Rituxan® is based only on *Roche*'s financial report. See *Biogen Inc. Annual Report on Form 10-k for the Year Ended December 31, 2018*, BIOGEN, INC. 63, <http://www.annualreports.com/> (last visited Jun. 28, 2019) (stating *Biogen*'s share of pre-tax profits in the U.S. for both Rituxan® and Gazyva® is US\$ 1,431.9 million in total; but not stating the revenue of each product individually). *Roche* listed Rituxan®'s U.S. sales as 4.29 billion in Swiss Franc (CHF), which is approximately US\$ 4.39 billion using the average US dollar Swiss Franc exchange rate in 2018. F. HOFFMANN-LA ROCHE, *supra* note 126; *Average Foreign Exchange Rates as per End of December 2018*, CREDIT SUISSE, <https://www.credit-suisse.com/> (last visited: Apr. 30, 2019).

132. Celgene Corporation [hereinafter as *Celgene*].

133. *Celgene Reports Fourth Quarter and Full Year 2018 Operating and Financial Results*, CELGENE CORP., <https://ir.celgene.com/> (last visited Jan. 31, 2019).

134. Bristol-Myers Squibb Company [hereinafter as *BMS*].

135. Pfizer, Inc. [hereinafter as *Pfizer*].

136. Eliquis®'s U.S. sales in 2018 was calculated by adding the sales revenue generated by *BMS* and *Pfizer*. *BMS* generated US\$ 3.76 billion in sales. *Bristol-Myers Squibb Reports Fourth Quarter and Full Year Financial Results*, BRISTOL-MYERS SQUIBB 11, <https://s21.q4cdn.com/> (last visited Jan. 24, 2019). *Pfizer* generated US\$ 1.849 billion in sales. *Appendix A 2018 Financial Report*, PFIZER, INC. 26, <https://s21.q4cdn.com/> (last visited Jun. 28, 2019).

## 2. Patent retrieval of the top three best-selling biologics in the U.S. based on 2018 sales revenue

### *a. In general*

The scope of this study is limited to U.S. granted patents and does not include U.S. patent applications or other patent-related documents outside of the U.S. The patent searches were done on April 30<sup>th</sup>, 2019 using the U.S. Official Patent Full Text and Image Database (hereinafter, USPTO patent database).

In order to identify possible keywords for the search queries, this study referenced information about the selected drugs from the U.S. Food & Drug Administration's "Drugs@FDA: FDA Approved Drug Products" database<sup>138</sup> (hereinafter, Drugs@FDA) and the "DrugBank" database<sup>139</sup> (hereinafter, DrugBank). The search queries included the names of the marketing company and its related subsidiary firm names; the name of the drugs; and fragmented or variations of mechanism-related keywords. Table 3 shows the search queries used for the patent search for the selected biologics and the count of hits these search queries have retrieved.

Anticipated patent expiration dates were retrieved through Google Patent Search<sup>140</sup> results or calculated using the USPTO patent term calculator<sup>141</sup> based on data retrieved from USPTO's public patent application information retrieval (hereinafter, "USPTO Public PAIR").<sup>142</sup>

Table 3: Biologic Patent Search Query and Count of Hits

<b>Brand Drug Name</b>	<b>Search Query in "Claims"</b>	<b>Search Query in "Assignee Name"</b>	<b>Number of Hits<sup>143</sup></b>
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137. PFIZER, INC., *supra* note 136, at 25.

138. *Drugs@FDA: FDA Approved Drug Products*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm>.

139. DRUGBANK, <https://www.drugbank.ca/> (last visited Jun. 28, 2019).

140. GOOGLE PATENTS, <https://www.google.com/?tbs=pts> (last visited Jun. 28, 2019).

141. *Patent Term Calculator*, U.S. PAT. & TRADEMARK OFF., [https://www.uspto.gov/sites/default/files/documents/patent\\_term\\_calculator.xls](https://www.uspto.gov/sites/default/files/documents/patent_term_calculator.xls). (last visited Jun. 28, 2019).

142. *USPTO Public Patent Application Information Retrieval*, U.S. PAT. & TRADEMARK OFF., <https://portal.uspto.gov/pair/PublicPair> (last visited Jun. 28, 2019).

143. The patents retrieved by these search queries are only raw data. Cross-examination of this raw data with other databases to include missed patents and to exclude irrelevant patents will further yield a final result for analysis.



Humira® <sup>144</sup>	“adalimumab” OR “TNF.alpha” OR “hTNF.alpha” OR “anti-TNF-alpha” OR “anti-TNF.alpha”	“AbbVie” OR “Abbott” <sup>145</sup> OR “BASF” <sup>146</sup>	178
Enbrel® <sup>147</sup>	“etanercept” OR “tumor necrosis factor receptor” OR “TNF receptor” OR “TNFR:Fc”	“Amgen” OR “Immunex” OR “Roche” OR “Hoffmann-LaRoche”	77

144. Approved by the FDA and marketed by *AbbVie* since 2002, Humira® (*AbbVie*'s brand name for adalimumab) is a monoclonal antibody for “the treatment of rheumatoid arthritis and other chronic debilitating diseases mediated by tumor necrosis factor.” *Adalimumab*, DRUGBANK, <https://www.drugbank.ca/drugs/DB00051#reference-A39984> (last visited Jun. 28, 2019); see Philip J. Mease, *Adalimumab in the Treatment of Arthritis*, 3 THERAPEUTICS & CLINICAL RISK MGMT. 133, 133–35 (2007). It is subcutaneously administered and available in a prefilled syringe form and in a convenient self-administrable pen form. See generally, Alan Kivitz & Oscar G. Segurado, *HUMIRA®Pen: A Novel Autoinjection Device for Subcutaneous Injection of the Fully Human Monoclonal Antibody Adalimumab*, 4 EXPERT REV. MED. DEVICES 109, 109–16 (2007). Humira binds with high specificity to tumor necrosis factor-alpha, or TNF-alpha, thereby inhibiting the interaction of TNF-alpha with p55 and p75 cell surface TNF receptors. Mease, *supra*. “TNF is a potent osteogenic cytokine and the central mediator of inflammation and joint destruction underlying RA [(rheumatoid arthritis)], PsA [(psoriatic arthritis)], and AS [(ankylosing spondylitis)] pathology.” *Id.* By blocking TNF interaction, Humira® alleviates cartilage and bone destruction in patients. See *id.*

145. *AbbVie* is a spin-off from Abbott Laboratories. See Abbott Laboratories, *Abbott Laboratories Completes Separation of Research-Based Pharmaceuticals Business*, BIOSPACE (Jan. 2, 2013), <https://www.biospace.com/>.

146. The reason to include “BASF” in the search query is that “Humira (D2E7, adalimumab) was originally developed through a joint venture between Cambridge Antibody Technology and BASF in the UK. . . . In 2000, Abbott acquired the pharmaceutical segment of the German chemical company, BASF, for \$6.9bn.” *Humira: The Highs and Lows of the World’s Best-Selling Drug*, PHARM. TECH. (Sep. 5, 2018), <https://www.pharmaceutical-technology.com/features/humira-abbvie-drug/>.

147. Marketed by *Amgen* since 1998, Enbrel® (brand name for etanercept) is a “[f]usion protein made up of 2 soluble TNF receptor molecule (TNFR1I) fused with the Fc fragment from human IgG1.” Mease, *supra* note 144. Similar to Humira®, Enbrel®, also targets TNF-alpha and thereby inhibits following cascades to inflammation. See *id.* Enbrel® “is indicated for the treatment of moderately to severely active rheumatoid arthritis in adults and chronic moderate to severe plaque psoriasis in adults.” *Etanercept*, DRUGBANK, <https://www.drugbank.ca/drugs/DB00005> (last visited Jun. 28, 2019).

	OR “TNFR”	OR “Hoffman-LaRoche” <sup>148</sup>	
Rituxan <sup>®149</sup>	“anti-CD 20” OR “anti-CD20” OR “rituximab”	“Genentech” OR “Biogen” OR “IDEC” OR “Roche” OR “Hoffmann-LaRoche” OR “Hoffman-LaRoche” <sup>150</sup>	69

148. The reason to include “Amgen”, “Immunex”, and “Hoffman-La Roche” in the search query is that there exist patents covering Enbrel<sup>®</sup> that were originally assigned to these entities. *See Enbrel<sup>®</sup> (etanercept) Patent Issued*, AMGEN (Nov. 22, 2011), <http://investors.amgen.com/phoenix.zhtml?c=61656&p=irol-newsArticle&ID=1633115> (“The patent [referring to U.S. Patent No. 8,063,182] is owned by Hoffman-La Roche Inc . . . and exclusively licensed to Amgen. Immunex Corporation (acquired by Amgen in 2002) originally licensed this patent application from Roche in 1999, and in 2004, Amgen paid Roche a one-time payment and obtained an exclusive, fully paid-up license to the application which issued today as the '182 patent. The patent describes and claims the fusion protein that is etanercept. . .”).

Notice that slight variations of the company name “Roche” were used in the search query. The reason is that the company name is often misspelled, even by those in the industry. *See, e.g., id.* (misspelling *Hoffmann-La Roche* as *Hoffman-La Roche*). The company name is “*Hoffmann-La Roche*” with two “n”s. *See Our History*, ROCHE, <https://www.roche.com/about/history.htm> (last visited Jun. 28, 2019) (“The founder of Roche, Fritz *Hoffmann-La Roche*, was a pioneering entrepreneur who was convinced that the future belonged to branded pharmaceutical products.” (emphasis added)).

149. Approved in 1997 and marketed by *Roche* and *Biogen*, Rituxan<sup>®</sup> is a chimeric monoclonal antibody and is directed against CD-20 antigens. Jason J. Emer & Claire Wolinsky, *Rituximab: A Review of Dermatological Applications*, 2 J. CLINICAL AESTHETIC DERMATOLOGY 29, 29 (2009). CD-20 is believed to play a crucial role in the regulation of cell-cycle initiation and differentiation of the B-cell lineage. *See id.* By binding to CD-20, Rituxan<sup>®</sup> mediates the lysis of B-cells through mechanisms including complement dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC). *Rituximab*, DRUGBANK, <https://www.drugbank.ca/drugs/DB00073#reference-A40017> (last visited Jun. 28, 2019). The indications of Rituxan<sup>®</sup> include Non-Hodgkin’s Lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA), etc. *Id.*

150. Rituxan<sup>®</sup> is marketed by *Biogen* and *Roche* in the U.S. Genentech Inc. was acquired by *Roche* in 2009. *See Andrew Pollack, Roche Agrees to Buy Genentech for \$46.8 Billion*, N. Y. TIMES (Mar. 12, 2009), <https://www.nytimes.com/2009/03/13/business/worldbusiness/13drugs.html>. *Idec Pharmaceuticals* was bought by *Biogen* in 2003 *See Andrew Pollack, Idec to Merge With Biogen in \$6.8 Billion Deal*, N. Y. TIMES (Jun. 24, 2003), <https://www.nytimes.com/2003/06/24/business/idec-to-merge-with-biogen-in-6.8-billion-deal.html>. The company name variations were used for the same reasons as described in note 148.

### *b. Inclusion of patents from other references*

For the purpose of ensuring the comprehensiveness of the patents retrieved, the search results were cross-examined with patents listed in complaints<sup>151</sup> against the biosimilar manufacturers. Patents that are listed on the complaints but not retrieved by the search query are added and included in the study.<sup>152</sup>

### *c. Exclusion of irrelevant patents*

To increase the accuracy of the search results, patents that merely claim the drugs or proteins as dispensable second therapeutic elements in dependent claims; or that claim the drugs or proteins targeting antigens or targets irrelevant to the drug of interest are excluded.

The collective set of patents covering each biologic after the inclusion of patents from other references and the exclusion of irrelevant patents are the final set of patents that undergoes analysis.

## 3. Patent retrieval of the top three best-selling small-molecule drugs in the U.S. based on 2018 sales revenue

### *a. In general*

The searches were conducted on April 30<sup>th</sup>, 2019 using the USPTO patent database and European Molecular Biology Laboratory (hereinafter, EMBL)'s SureChEMBL<sup>beta</sup> Open Patent Data<sup>153</sup> (hereinafter, SureChEMBL). For the patent searches in the USPTO patent database, drug names, fragmented structure names (IUPAC structure names), names of the marketing company and its related subsidiary firm names were used as keywords in the search query. In order to identify appropriate keywords, information from the Drugs@FDA and DrugBank were also used as references. For the structural searches in SureChEMBL, search results were limited to exact structures of the drug molecules. Table 4 lists the search

151. To find the relevant complaints a case search was done using the PORTAL database built by Unified Patents Inc. PORTAL, <https://portal.unifiedpatents.com/> (last visited Jun. 28, 2019). The brand drug company names were used as the search query in the plaintiff field. The patents-in-suit in the retrieved cases were cross-examined with the patent search results.

152. The reason why some of the patents listed on the complaints are not retrievable by the search query is because these patents claim fundamental manufacturing aspects of the drug or protein. Therefore, these patents do not necessarily claim specific manufacturing process of a particular drug or protein and are consequently out of the scope of the search queries that target specific antibodies or proteins.

153. SURECHEMBL<sup>BETA</sup> OPEN PATENT DATA, <https://www.surechembl.org/search/> (last visited Jun. 28, 2019).

queries used to search for patents covering each small-molecule drug and the count of hits the search queries have retrieved.

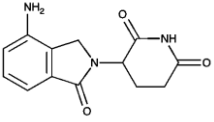
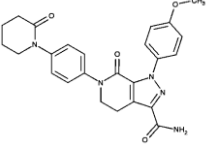
Expected patent expiration dates were also retrieved through Google Patent Search results or calculated using the USPTO patent term calculator based on data retrieved from USPTO Public PAIR.

Table 4: Small-Molecule Patent Search Query and Count of Hits

Brand Drug Name	Database	Search Query in “Title”, “Abstract” and “Claims”	Search Query in “Assignee Name”	Number of Hits <sup>154</sup>
Revlimid <sup>®155</sup>	USPTO patent database	“3- 4-amino-1-oxo-1,3-dihydroisoindol-2-yl - piperidine-2,6-dione” OR “4-amino-1-oxo-1,3 dihydroisoindol-2-yl” OR “lenalidomide” OR “3- (4-amino-1-oxo-1,3-dihydroisoindol-	Celgene	59

154. The patents retrieved by these search queries are only considered preliminary results. Cross-examination of the preliminary results with other databases to include missed patents and to exclude irrelevant patents will further yield a final result for analysis.

155. Revlimid<sup>®</sup>, *Celgene*'s brand name for lenalidomide, is an analogue of thalidomide and an immunomodulator. Martin Paspe Cruz, *Lenalidomide (Revlimid) A Thalidomide Analogue in Combination With Dexamethasone For the Treatment of All Patients With Multiple Myeloma*, 41 PHARM & THERAPEUTICS 308, 308 (2016). The drug has multiple mechanisms of actions, including the stimulation of the immune system, the inhibition of cell proliferation in tumor cells and the attenuation of angiogenesis. *Mechanism of Action*, REVLIMID.COM, <https://www.revlimid.com/mm-hcp/mechanism-of-action/?mm-self-id=yes> (last visited Jun. 28, 2019). It has been demonstrated, *in vitro*, that lenalidomide inhibits the expression of cyclooxygenase-2 (COX-2). *Lenalidomide*, DRUGBANK, <https://www.drugbank.ca/drugs/DB00480> (last visited Jun. 28, 2019). Revlimid<sup>®</sup> was approved by the FDA in 2005 and was “initially intended as a treatment for multiple myeloma . . . but has also shown efficacy in the hematological disorders known as the myelodysplastic syndromes.” *Id.*

		2-yl) -piperidine-2,6-dione” <sup>156</sup>		
	SureChEMBL			61
Eliquis <sup>®157</sup>	USPTO patent database	“apixaban” OR (4-methoxyphenyl\$ AND “pyrazolo[3,4-c]pyridine-3-carboxamide”)” <sup>158</sup>	“Bristol-Myers Squibb” OR “Pfizer” <sup>159</sup>	8
	SureChEMBL			3
Lyrica <sup>®160</sup>	USPTO	“pregabalin”	“Warner-	46

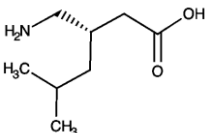
156. The IUPAC name of Revlimid<sup>®</sup> is “3-(4-amino-1-oxo-2,3-dihydro-1H-isoindol-2-yl)piperidine-2,6-dione.” DRUGBANK, *supra* note 155. To retrieve more comprehensive results, search queries included fragmentations of its IUPAC name.

157. Eliquis<sup>®</sup> is the brand name of the drug apixaban. It is an “oral direct factor Xa inhibitor that has been shown to reduce the risk of stroke in a similar population in comparison with aspirin.” Christopher B. Granger et al., *Apixaban Versus Warfarin in Patients with Atrial Fibrillation*, 365 NEW ENG. J. OF MED 981, 981 (2011). Eliquis<sup>®</sup> was approved in 2012 and is indicated for “reducing the risk of stroke and systemic embolism in patients who have nonvalvular atrial fibrillation, prophylaxis of deep vein thrombosis (DVT) leading to pulmonary embolism (PE) . . . and treatment of DVT and PE to reduce the risk of recurrence.” *Apixaban*, DRUGBANK, <https://www.drugbank.ca/drugs/DB06605> (last visited Jun. 28, 2019). Besides factor Xa, Eliquis<sup>®</sup> also inhibits prothrominase. *Id.* Collectively, they prevent the formation of thrombus. *Id.*

158. The IUPAC name of Eliquis<sup>®</sup> is “1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-1H,4H,5H,6H,7H-pyrazolo[3,4-c]pyridine-3-carboxamide.” DRUGBANK, *supra* note 157. The fragmented name was used in the search query to obtain more comprehensive results. *Cf. supra* note 156. The symbol “\$” refers to a wildcard when searching in the USPTO patent database. *See Help on the Advanced Search Page*, U.S. PAT. & TRADEMARK OFF., PAT. FULL TEXT & IMAGE DATABASE, <http://patft.uspto.gov/metahtml/PTO/help/helpadv.htm> (last visited Jun. 28, 2019).

159. To ensure that all possible patents were retrieved by the marketing companies, both *BMS* and *Pfizer* were used in the search query. *See BRISTOL-MYERS SQUIBB, supra* note 136; *see also PFIZER, INC., supra* note 136.

160. Lyrica<sup>®</sup> is the brand name for the drug pregabalin. It is approved for “adjunctive therapy of partial seizures in adults, and has [also] been approved for the treatment of pain from diabetic neuropathy or post-herpetic neuralgia in adults.” Charles P. Taylor, *Pharmacology and Mechanism of Action of Pregabalin: The Calcium Channel 2—(alpha2—delta) Subunit as a Target for Antiepileptic Drug Discovery*, 73 EPILEPSY RES. 137, 137 (2007). There are currently “two types” of Lyrica<sup>®</sup>: the original version—Lyrica<sup>®</sup>—and its extended release, Lyrica CR<sup>®</sup>. The primary patents of the original

	patent database	OR “5- methylhexanoic” 161	Lambert” OR “Pfizer” <sup>162</sup>	
	SureChEMBL			46

*b. Inclusion of patents from other references*

In order to increase the comprehensiveness of the study, the search results were cross-examined with patents listed in complaints<sup>163</sup> against the drug’s generic manufacturers. Furthermore, the search results were also cross-examined with the patents listed in the U.S. Food and Drug Administration’s “Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations” (hereinafter, “the *Orange Book*”)<sup>164</sup> and the patent information listed in DrugBank.

version of Lyrica® (U.S. Patent No. 6,001,876 and U.S. Patent No. 6,197,819) were set to expire at the end of 2018 just when the FDA approved Lyrica CR®. Lyrica CR® is covered by patents whose expiration dates extend beyond 2026. (According to the Orange Book, the latest patent expiration date for Lyrica CR® is set on Nov. 2, 2026, but with pediatric extension, the expiration of the exclusivity is set to be on May 2, 2027). Lyrica CR® is merely an extended release of Lyrica® (and even covered by the same patent, *see, e.g.*, U.S. Patent No. RE41,920 (which is listed as a patent covering both Lyrica® and Lyrica CR®)). The difference between the drugs is that instead of taking the pill three times a day (Lyrica®), patients could take the pill once a day (Lyrica CR®). *See* Eric Sagonowsky, *With a Year Left Before Generics Hit, Pfizer Nabs FDA Approval for New-and-Improved Lyrica*, FIERCEPHARMA (Oct. 12, 2017), <https://www.fiercepharma.com/>. For patent comparison purposes, the article will treat the drug collectively as Lyrica®.

161. The IUPAC name of Lyrica® is “(3S)-3-(aminomethyl)-5-methylhexanoic acid.” *Pregabalin*, DRUGBANK, <https://www.drugbank.ca/drugs/DB00230> (last visited Jun. 28, 2019). The fragmented name was used in the search query to obtain more comprehensive results. *Cf.* DRUGBANK, *supra* note 156.

162. Some of Lyrica®’s patents originally belonged to Warner-Lambert Company (*See, e.g.*, U.S. Patent No. 8,945,620; U.S. Patent No. 10,022,447), which was acquired by Pfizer in 2000. Laura M. Holson & Melody Petersen, *Pfizer and Warner-Lambert Are Seen in Merger Deal*, N. Y. TIMES (Feb. 3, 2000), <https://www.nytimes.com/>.

163. To find the relevant complaints, a case search was done using the PORTAL database built by UNIFIED PATENTS INC. PORTAL, <https://portal.unifiedpatents.com/> (last visited Jun. 28, 2019). The brand drug company names were used as the search query in the plaintiff field. The patents-in-suit in the retrieved cases were cross-examined with the patent search results.

164. *U.S. Food & Drug Admin. ’s Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations*, U.S. FOOD & DRUG ADMIN., <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm> (last visited Jun. 28, 2019).

### c. Exclusion of irrelevant patents

Patents that merely claim the drug as a dispensable second therapeutic element in dependent claims or that claim other molecule structures are excluded.

The collective set of patents covering each small-molecule drug after the inclusion of patents from other references and the exclusion of irrelevant patents are the final set of patents that undergoes analysis.

### 4. Core patents and peripheral patents

In order to better present and analyze the alleged patent thickets, this article proposes a patent portfolio visualization for the selected drugs. The reasoning behind this visualization can be explained in Figure 1.

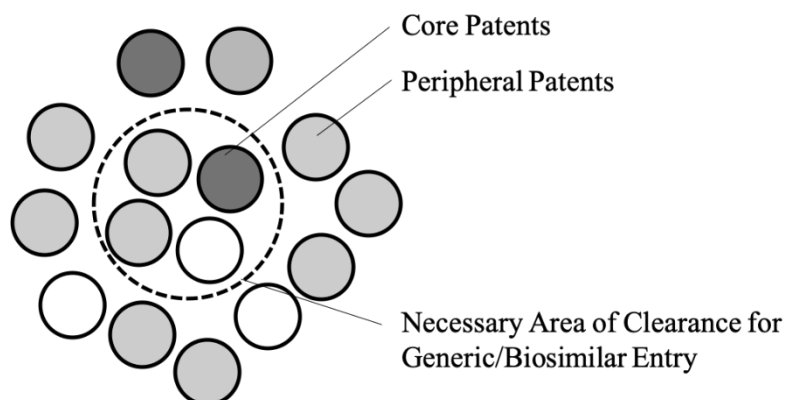


Figure 1. Hypothetical Drug Patent Portfolio Visualization

Source: own construction.

Figure 1 is a hypothetical example of the proposed patent portfolio visualization. The circles represent patent scopes of each patent that potentially covers the drug; while the different shades of gray filling the circles symbolize different types of patents.<sup>165</sup> The dashed circular area is the necessary scope of patent “clearance” for generic or biosimilar entry. That is, the patents (circles) within in the dashed circular area are those that will block generic or biosimilar entry and are thus considered the “core patents.” The other drug patents outside of the dashed circular area only

<sup>165</sup> The types of patents include composition of matter patents, treatments patents, manufacturing patents, formulation patents and etc. See Figure 2, *infra*.

cover aspects of the drug that are not necessarily essential for generic or biosimilar entry. These patents are thus termed “peripheral patents.” Examples of “peripheral patents” include patents that cover drug polymorphs that are not approved by the FDA,<sup>166</sup> devices that assist in administering the drug,<sup>167</sup> or methods to monitor or predict the treatment of the drug.<sup>168</sup>

In this study, patents that are listed in complaints, on patent lists provided by brand biologic companies and on the Orange Book are considered “core patents;” since these patents are those that were asserted or that the brand name drug companies believe a claim of patent infringement could reasonably be asserted against biosimilar and generic drug applicants.<sup>169</sup> The remaining retrieved patents are considered “peripheral patents.”

166. *E.g.*, U.S. Patent No. 8,143,286; U.S. Patent No. 8,431,598; U.S. Patent No. 8,822,499; U.S. Patent No. 9,353,080; U.S. Patent No. 9,365,538; U.S. Patent No. 9,371,309 (all claiming polymorphs of the small-molecule drug Revlimid<sup>®</sup>).

167. *E.g.*, U.S. Patent No. 8,992,476; U.S. Patent No. 9,408,973; U.S. Patent No. 9,943,649 (all claiming an autoinjection device for the administration of Humira<sup>®</sup>).

168. *E.g.*, U.S. Patent No. 8,728,730 (relating to a method for the prediction of the treatment of rituximab).

169. *See* 42 U.S.C. §262 (I)(3)(A)(i) (stating that the reference product sponsor should provide a patent list “for which the reference product sponsor believes a claim of patent infringement could *reasonably be asserted* by the reference product sponsor, or by a patent owner that has granted an exclusive license to the reference product sponsor with respect to the reference product, if a person not licensed by the reference product sponsor engaged in the making, using, offering to sell, selling, or importing into the United States of the biological product that is the subject of the subsection (k) [or the biosimilar] application” (emphasis added)); for small-molecule drugs, *see* 21 C.F.R. § 314.53 (b)(1) (stating that the patents on the Orange Book should be patents that “claims the drug or a method of using the drug that is the subject of the NDA or amendment or supplement to it and with respect to which a claim of patent infringement could *reasonably be asserted* if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.”).

Note that due to the very nature of them being bio-“*similar*,” the scope of patent clearance required for entry may vary slightly for different biosimilars. For example, the number of patents the reference sponsor identified as potentially infringed is different for different biosimilar companies. *Cf.* Complaint at 13-15, *AbbVie Inc. et al v. Amgen Inc. et al*, CIVIL No. 1:16-cv-00666-UNA (D. Del. Aug. 2, 2017) (No. 1) (MaxVal Litigation Databank) (alleging possible infringement of 61 patents) *with AbbVie v. BI complaint*, at 15-19 (wherein same plaintiff alleging possible infringement of 74 patents against a different biosimilar manufacturer.). Therefore, compared to small-molecule generics, the patent scope clearance required for entry (or what patents constitute as the core patents) for each individual biosimilar claiming the same reference product may vary at a larger extent. *See, e.g.*, Steve Brachmann, *Bristol-Myers Squibb, Pfizer File ANDA Lawsuits Against Makers of Generic Eliquis*, IPWATCHDOG (Apr. 12, 2017), <https://www.ipwatchdog.com/> (stating that *BMS* and *Pfizer* “fired off a series of nine lawsuits to prevent generic versions of Eliquis,” wherein the patents asserted were the two patents: U.S. Patent No. 6,967,208 and U.S. Patent No. 9,326,945.).

However, despite the possible differences in what are considered as the “core patents for *each* biosimilar claiming the *same* reference product,” this article treats the union of these patents (including all patents on exchange lists and complaints) as the “core patents” of the biologic henceforth in this article. Reasons that lead to this decision as well as what limitations the decision will entail are discussed as follows.



The visualization of Figure 1 is further simplified to the form in Figure 2. The center pie chart in Figure 2 presents the number of core patents categorized by the drug aspects they cover—including the composition of matter<sup>170</sup>; the treatments, the formulations, the manufactures and other aspects<sup>171</sup>; while the outer donut chart shows the number of peripheral patents using the same categorization. The form illustrated in Figure 2 not only helps in the spatial visualization of “core patents” and “peripheral patents” but also provides the patent counts and statistical numbers about the patent portfolio. Moreover, the size of each improved patent portfolio visualization is proportional to the number of patents in the portfolio.

First, it is practically impossible to know what patents will be considered as the “core patents” for the following potential biosimilar applicants. The next potential applicant may have found a way to circumvent patents that are “core patents of previous biosimilars” or fail to circumvent patents that are “peripheral patents of previous biosimilars.” Thus, for the sake of providing historic references for future possible biosimilars, treating the “core patents for previous biosimilars” collectively as the “core patents” of the biologic would be reasonable. Readers may argue why this article does not treat the *intersection* of “the core patents for previous biosimilars” as the “core patents” of the biologic and treat the remainder as “peripheral patents.” Based on the fact that at least one previous biosimilar applicant is unable or is believed by the reference sponsor to be unable to circumvent these patents (the union of patents listed on all complaints and exchange lists) indicates that theoretically, at least significantly more effort is required to design around these patents in comparison to those not listed, even if these patents may not claim the most essential part of the biologic. Admittedly, whether a patent truly does block biosimilar or generic entry warrants litigation scrutiny. Thus, strictly speaking, patents listed on complaints, in exchange lists or in the Orange Book do not necessarily mean that they are the “core patents” that will result in injunction and thus block market entry. Nevertheless, since they *are* listed, biosimilars and generics do need to at least put in the effort to prove non-infringement or patent invalidity. Thus, broadly speaking, listed patents do hinder the entry of biosimilars and generics.

Another issue worth emphasizing is that not all “core patents” cover the reference biologic product itself. This is because there can be patents that would block biosimilar entry by claiming a variation of the reference biologic product. In other words, these patents claim the “wiggling room” between biosimilars and biologic reference products. *See, e.g., BI’s Motion for Leave to File Amended Answers* at 64 (arguing that “[a]t least nine of AbbVie’s formulation patents in the Humira® patent scheme *do not* contain even one claim that reflects the Humira® formulation. U.S. Patent No. 8,795,670, 9,327,032, and U.S. Patent No. 9,732,152, for example, sought to patent the use of, but the Humira® formulation does not include histidine . . . .”) This issue will also be further discussed in the causes of patent thickets and the solutions thereof. *See infra* Part VI.B.2. & VII.A.2.

170. For example, patents that cover the drug itself or its sequence variations or polymorphs.

171. The “other aspects” category includes patents covering the diagnostic methods, the devices or patents having multiple aspects in one patent.

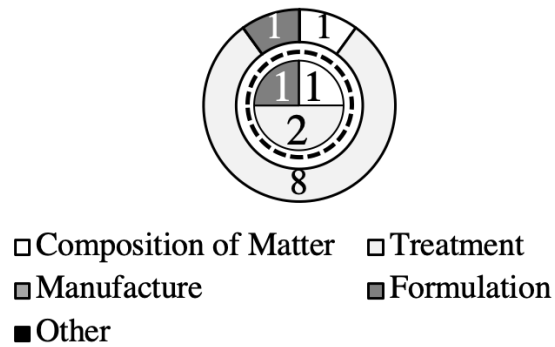


Figure 2. Improved Hypothetical Drug Patent Portfolio Visualization

Source: own construction.

#### *D. Research Results: Patent Portfolio Visualization*

The patent portfolio visualizations of each selected drug are presented (Figures 3-8). As explained in previous sections, the outer donut chart represents the peripheral patents while the center pie chart represents the core patents. The relative sizes of the patent portfolio visualizations are proportional to the number of patents.

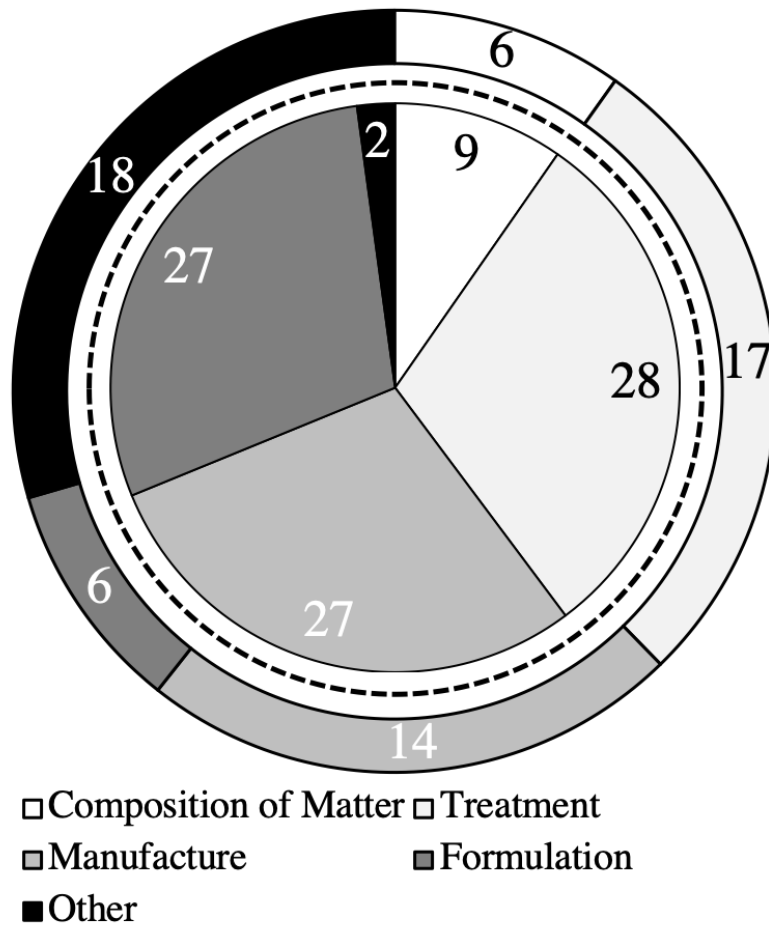


Figure 3: Humira®'s Patent Portfolio Visualization  
 Source: own construction based on patents retrieved in empirical study.

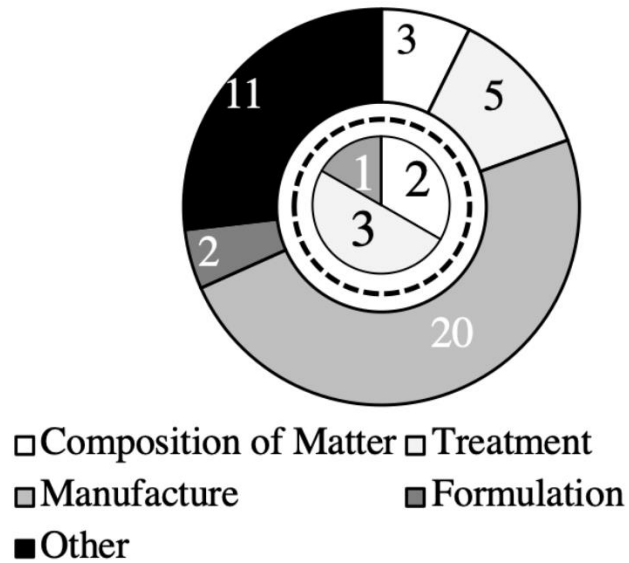


Figure 4: Enbrel<sup>®</sup>'s Patent Portfolio Visualization  
 Source: own construction based on patents retrieved in empirical study.

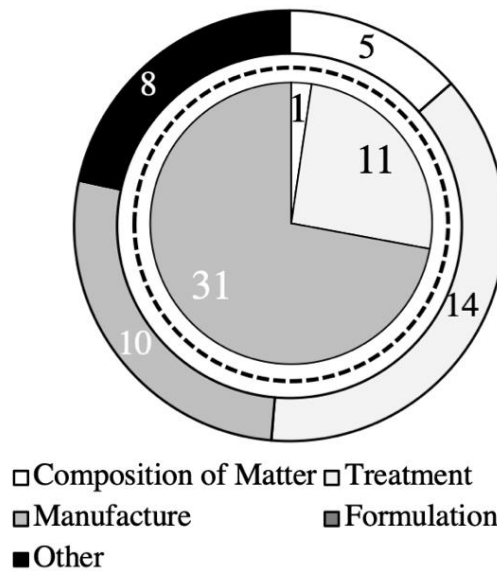
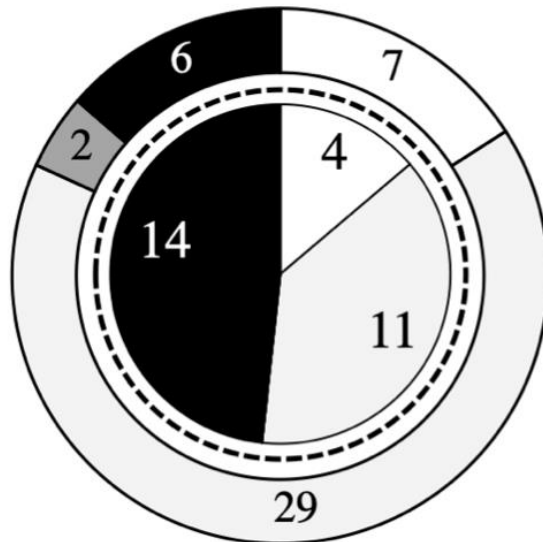
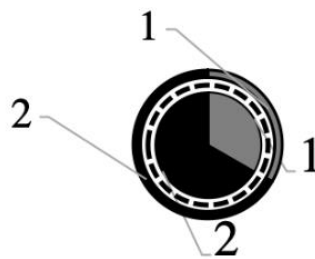


Figure 5: Rituxan<sup>®</sup>'s Patent Portfolio Visualization  
 Source: own construction based on patents retrieved in empirical study.



- Composition of Matter
- Treatment
- Manufacture
- Formulation
- Other

Figure 6: Revlimid®'s Patent Portfolio Visualization  
 Source: own construction based on patents retrieved in empirical study.



- Composition of Matter
- Treatment
- Manufacture
- Formulation
- Other

Figure 7: Eliquis®'s Patent Portfolio Visualization  
 Source: own construction based on patents retrieved in empirical study.

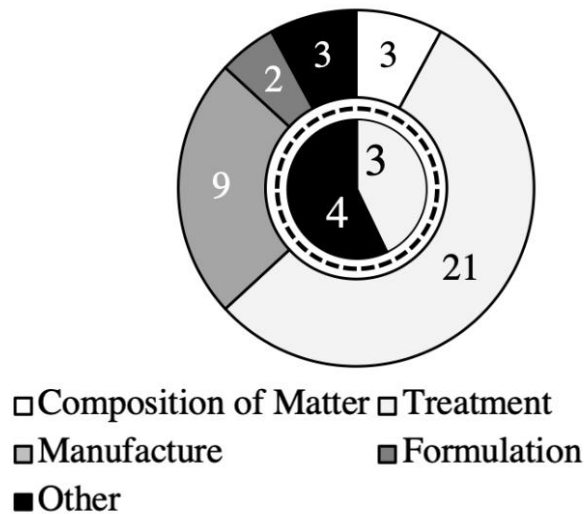


Figure 8: Lyrica®'s Patent Portfolio Visualization  
Source: own construction based on patents retrieved in empirical study.

#### *E. Preliminary Assessment of Patent Thickets*

Previous literature has proposed different methods to measure the extent of patent thickets.<sup>172</sup> However, most of this literature bases their measurements on the definition that the patents in the alleged patent thicket belong to multiple firms.<sup>173</sup> This definition does not apply to the case of this study as the commercialization of biosimilars and generics mainly depend on the elimination of patents belonging to one or two branded drug companies. Moreover, these studies have only focused on patent thickets that cover a specific technological area instead of a single particular product.<sup>174</sup> Therefore, the methods employed by these studies are not suitable for the present study. In this Section, this article explores two

172. BRONWYN H. HALL ET AL., A STUDY OF PATENT THICKETS 37-40 (2013), <https://assets.publishing.service.gov.uk/>.

173. For example, the social network analysis by using the concept of triplets—“defined as a group of three firms in which each firm has critical prior art limiting claims on recent patent applications of each of the other two firms.”—; or “measuring the hold-up potential existing in different parts of the patent system using qualitative techniques such as interviews.” *See id.*

174. *See, e.g., id.* at 41-42 (showing the triplet counts of different technological areas); *see generally*, Gave Clarkson & David DeKorte, *The Problem of Patent Thickets in Convergent Technologies*, 1093 ANNALS N. Y. ACAD. SCI. 180, 180-200 (2006) (focusing on nanotechnology); *see generally*, Charlie Schmidt, *Negotiating the RNAi Patent Thicket*, 25 NATURE BIOTECH. 273, 273-75 (2007) (focusing on RNAi).

preliminary ways to assess drug patent thickets. Based on the two proposed preliminary assessment methods, results show that biologics have a greater tendency to form patent thickets.

## 1. Patent counts as criterion

### *a. Reasoning of analysis*

As discussed previously, a patent thicket is a dense web of overlapping patents covering a single technology that a company must plow through to actually commercialize the technology.<sup>175</sup> If we define the “single technology” the alleged patent thicket covers as the product, or in the case of this article, the drug, the patents that cover the drug would then be considered the alleged patent thicket. Thus, it would be reasonable to use the counts of these patents to assess Type I Patent Thickets.<sup>176</sup> The idea behind this assessment is that whenever a competitor hopes to fully commercialize the drug, it would then have to hack through, for example, the patents that cover the active drug ingredient itself, the different steps of manufacture, the treatments of uses, or even combinational uses and devices to administrate the drug, all of which overlapping the “single technology”—the “drug.” Table 5 lists the final patent counts<sup>177</sup> of the selected drugs.

### *b. Analysis of patent counts*

According to the results illustrated in Table 5, the drugs having the top two highest total patent counts are both biologics—Humira<sup>®</sup> and Rituxan<sup>®</sup>, each having 154 patents and 80 patents, respectively. Ranking third is the

175. *See, supra* Part III.A.

176. Of course, “patent counts” is not the only method to assess the extent of patent thickets. Patent claims, which represent a certain embodiment of the invention could also be used as a criterion. However, the number of claims may not necessarily indicate how much “effort” or how “dense” the patent thicket is as the scope of different patent claims are hardly the same. It is possible that the scope of a single claim in one patent is many times broader or harder to handle for alleged infringers than another claim in another patent.

Another anticipated question would be: why not use the patent scope of each patent claim as criterion for patent thicket assessment? The problem with this proposal is the comparative scope size for different patent claims is not easily defined. The determination process would also be very subjective and arguably less persuasive. Thus, to avoid complication, this study will conveniently use patent counts as the main criterion for assessment. Although patents arguably have the same “scope” problem as patent claims have, a patent covers only one single invention. 35 U.S.C. § 101. Therefore, using patent counts as assessment criterion at least provides the picture of how many “patented inventions” the competitor-to-be needs to hack through to commercialize the technology.

177. The preliminary results were cross-examined with different databases to yield a final result for analysis. *See, supra* notes 143 and 154.

small-molecule drug Revlimid<sup>®</sup>, with 74 patents in total. The remaining drugs all have fewer than 50 granted U.S. patents.

However, from an entry barrier perspective and assuming that potential competitors are not planning to commercialize every aspect of the drug, the core patents are what primarily prevents entry. By comparing core patent counts, the ranking is somewhat similar to the ranking of total patent counts.

Comparing both total and core patent counts of the top-selling drugs show that biologics accumulate more patents compared to small-molecule drugs—indicating the presence of patent thickets.

Table 5: Core and Peripheral Patent Counts of the Selected Drugs

Source: own calculation based on patents retrieved in empirical study.

<b>Brand Drug Name</b>	<b>Drug Category</b>	<b>Core Patent Count</b>	<b>Peripheral Patent Count</b>	<b>Total</b>
Humira <sup>®</sup>	Biologic	93	61	154
Rituxan <sup>®</sup>	Biologic	43	37	80
Revlimid <sup>®</sup>	Small-Molecule	29	44	73
Enbrel <sup>®</sup>	Biologic	6	41	47
Lyrica <sup>®</sup>	Small-Molecule	7	38	45
Eliquis <sup>®</sup>	Small-Molecule	3	3	6

## 2. Adding time into perspective

### *a. Reasoning of analysis*

Patents expire.<sup>178</sup> Thus, if we only consider patent counts, we may overstate the number of patents generic or biosimilar need to clear for market entry. It is possible that the patents covering the drug span across a

178. 35 U.S.C. § 154 (a)(2).



long period and do not amount to a patent thicket at any given time point. In this radical scenario, the competitors would not need to hack through as many patents as in a scenario where the same number of patents is concentrated in a shorter time period.<sup>179</sup> Thus, to incorporate the “time” element in the patent thicket assessment, figures that present active core and peripheral patent counts at different time points are constructed for each drug.<sup>180</sup>

In order to calculate the number of active patents at a given timepoint for a selected drug, the number of core or peripheral patents applied before such given time point is subtracted with the anticipated number of core or peripheral patents expired before such given time point.<sup>181</sup> For graphing purposes, the time points are all set at the end of each year.<sup>182</sup> The counts of active patents between each time points are treated continuously to form an “active patent count-time plot.”<sup>183</sup>

179. In the scenario which multiple patents covering a single drug span across a long period might amount to patent evergreen. *See, supra* Part III.A.

180. *See* Figures 9-14, *infra*.

181. To effectively compare the 20-year patent term, the patent application date and the expiration date are used to define the term of an “active patent” even though patents rights are received only once they are issued. 35 U.S.C. § 154 (a)(2). *But see id.* § 154 (d) (provisional rights).

182. Due to using each “year” rather each “day” as the individual time points, patents applied or expired at different times within the same year are all viewed as applied or expired at the end of such given year. Therefore, the plot does not account for the change of active patent counts within a single year.

183. Though providing a more accurate picture of patent thickets compared to patent counts, using active patent count vs. time plots for assessment is based on some assumptions that may require some attention. These assumptions, depending on whether they are true or on their extent, may overestimate or underestimate the degree of patent thickets.

First, the study is limited to granted patents and does not include patent applications. This limitation may result in an underestimation of the extent of patent thickets; since if the pending patent applications are subsequently granted, the newly granted patents may add to the alleged patent thicket. Another possibility of underestimation is the calculation of patent expiration dates. Although patent terms are calculated 20 years from the earliest claimed non-provisional domestic application, it is possible that the applicant is not claiming benefit from the first filed application. In this case, the expiration date may actually be later than anticipated. This may contribute to a longer year span and result in a larger extent of patent term overlap. Furthermore, there can still be patents that potentially cover the drug but are not included in the study due to them not being retrievable through the present research method.

When it comes to the possibilities of overstating the extent of patent thickets, the assessment treats all patents as equally valid, important and indispensable of the drug. This assumption does not consider the fact that patents applied later are possibly easier to design around. If this were true, the patent thicket may not be as hard to hack through as it seems. Moreover, the assessment also treats the alleged patent thicket as being intact. It does not take into the account that patents may expire earlier due to failing to pay maintenance fees or be deemed unenforceable or unpatentable by courts or the Patent Trial and Appeal Board (hereinafter, PTAB).

*b. Active patent count vs. time plot of selected drugs*

The active patent count-time plots of the selected drugs are presented herein (Figures 9-14). For comparison reasons, the maximum value of the y-axis (patent counts) is set at 160. The year of U.S. market entry of each selected drug is labeled on the figures as well.

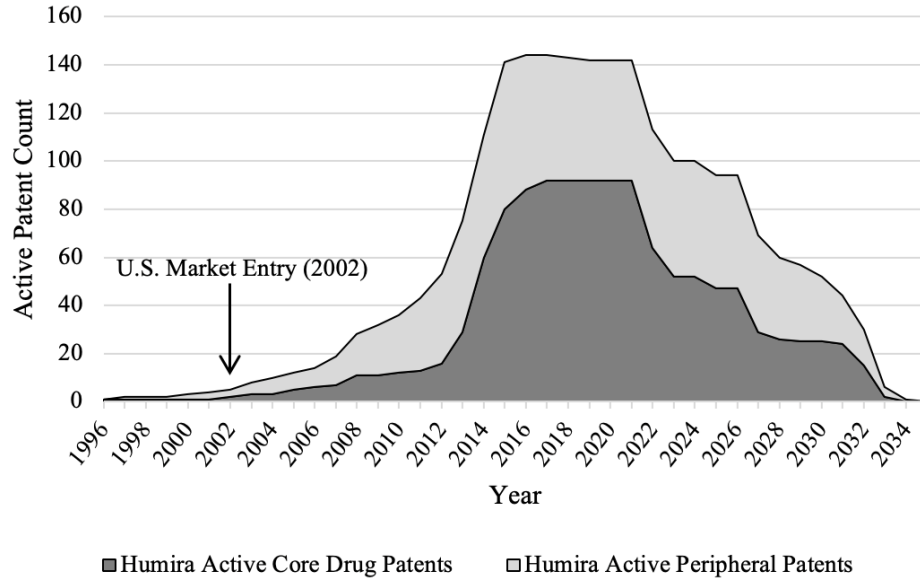


Figure 9: Humira®’s Active Patent Counts by Year  
 Source: own construction based on patents retrieved in empirical study.

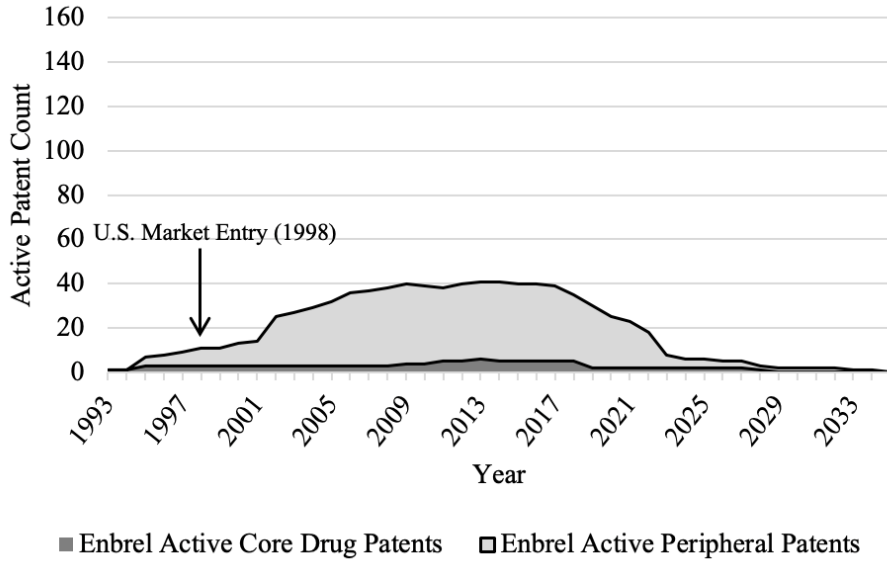


Figure 10: Enbrel®’s Active Patent Counts by Year  
 Source: own construction based on patents retrieved in empirical study.

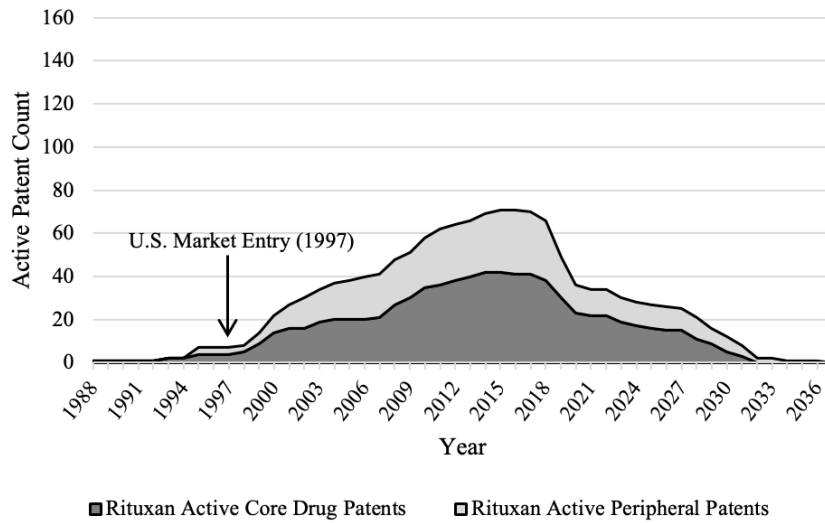


Figure 11: Rituxan®’s Active Patent Counts by Year

Source: own construction based on patents retrieved in empirical study.

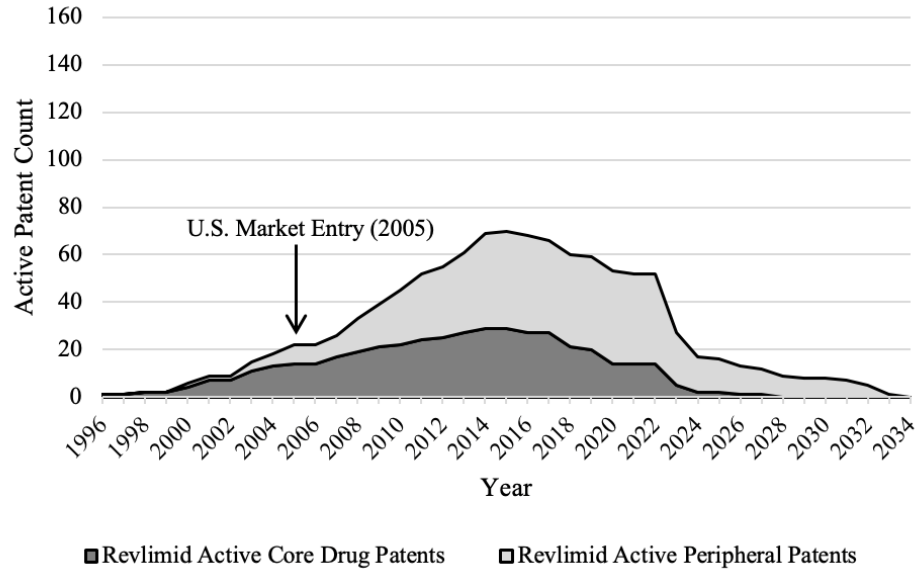


Figure 12: Revlimid®'s Active Patent Counts by Year  
 Source: own construction based on patents retrieved in empirical study.

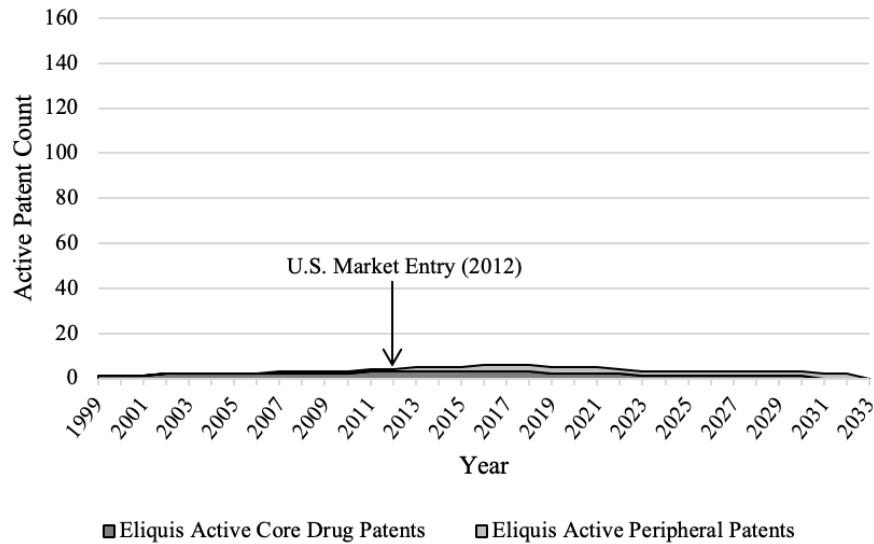


Figure 13: Eliquis®'s Active Patent Counts by Year

Source: own construction based on patents retrieved in empirical study.

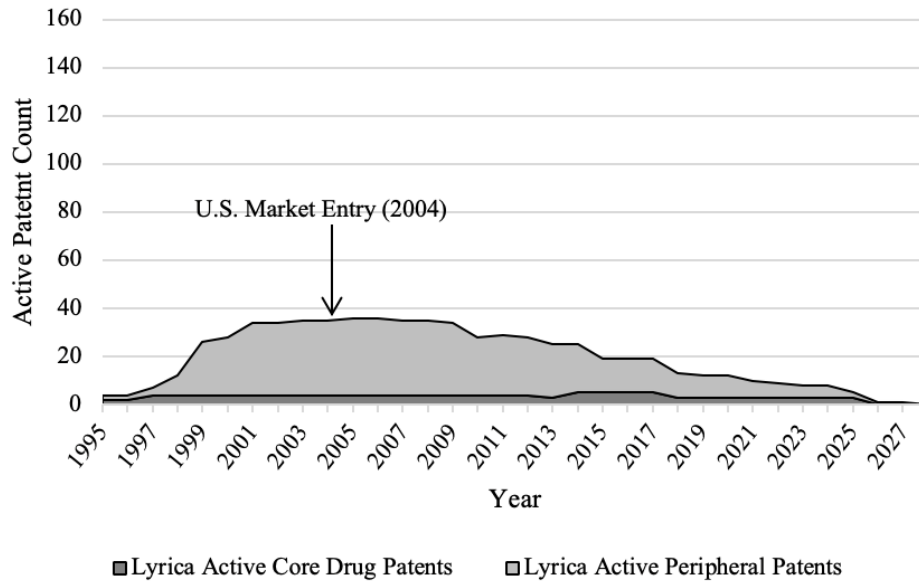


Figure 14: Lyrica®’s Active Patent Counts by Year

Source: own construction based on patents retrieved in empirical study.

*c. Analysis of active patent count vs. time plots*

For comparison and analytical reasons, the core active patent counts from Figures 9-14 are consolidated to construct Figure 15. Similarly, the total active patent counts from Figures 9-14 are consolidated to construct Figure 16. The peak and average active patent counts of the selected drugs are presented in Table 6.

According to the results from Table 6, we can unquestionably see that Humira® ranks first place in all indicators, including peak and average counts of both core and total patents. Coming in second in the indicators of core patents is Rituxan®, making the top two drugs in core patent counts both biologics. Noticeably, Rituxan® and the small-molecule drug Revlimid® have very similar peak and average patent counts when considering both core and peripheral patents.

In sum, the results show that when considering both core and peripheral patents, it can arguably be said that the difference in average counts is less significant. However, if we consider only core patents,

patents that necessarily block market entry, biosimilar companies do face more barriers compared to small-molecular drug companies.

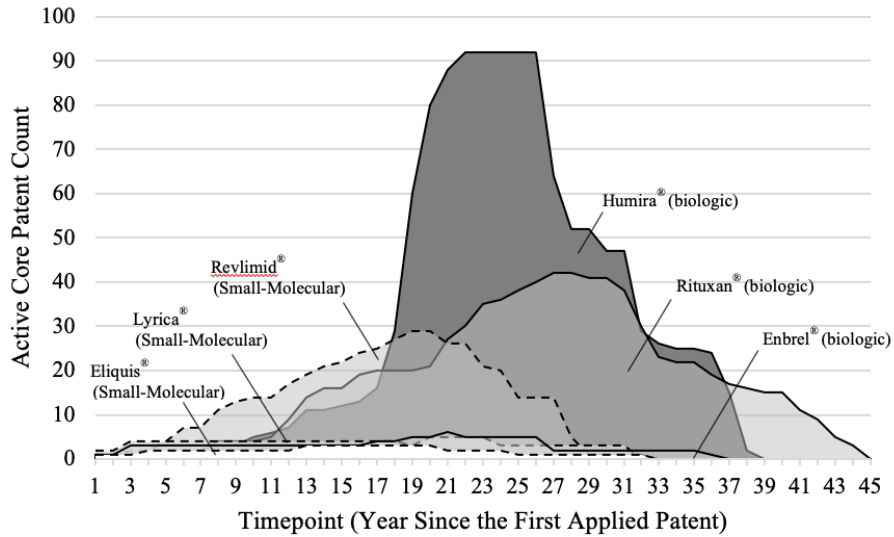


Figure 15: Active Core Patent Count vs. Time Plots of Selected Drugs  
Source: own construction based on patents retrieved in empirical study.

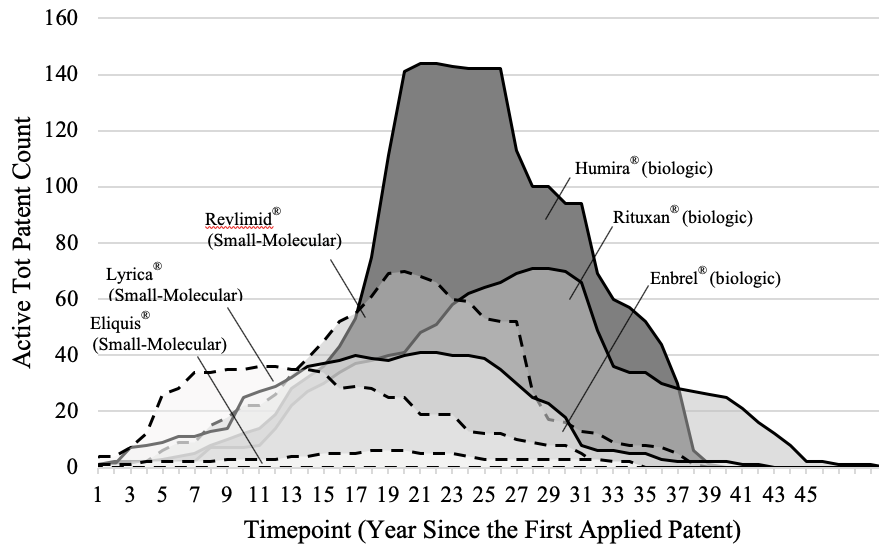


Figure 16: Active Total Patent Count vs. Time Plots of Selected Drugs  
Source: own construction based on patents retrieved in empirical study.

Table 6: Peak and Average Active Patent Counts of the Selected Drugs  
Source: own calculation based on patents retrieved in empirical study.

<b>Brand Drug Name</b>	<b>Drug Category</b>	<b>Peak (Core)<sup>184</sup></b>	<b>Average (Core)</b>	<b>Peak (Total)<sup>185</sup></b>	<b>Average (Total)</b>
Humira <sup>®</sup>	Biologic	92	31.28	144	56.95
Rituxan <sup>®</sup>	Biologic	42	17.73	71	27.40
Revlimid <sup>®</sup>	Small-Molecule	29	13.12	70	27.85
Enbrel <sup>®</sup>	Biologic	6	3.20	41	19.33
Lyrica <sup>®</sup>	Small-Molecule	5	3.59	36	19.59
Eliquis <sup>®</sup>	Small-Molecule	3	1.85	6	3.23

#### IV. TYPE I AND TYPE II BIOLOGIC PATENT THICKETS

Though having provided the patent counts of the alleged patent thickets, the study does not stop here. This article further argues that there are actually *two* types of patent thickets. As the following Parts entail, the two types of patent thickets are different in nature; the impacts they contribute; and the causes that give rise to them. It would be irresponsible to treat and assess the two types of patent thickets as one.

In this Part, Section A first discusses the reasoning behind the differentiation of the two types of patent thickets. Next, Section B proposes a method to identify the two types of patent thickets. Armed with the method, this article then assesses the extent of the two types of patent thickets in the core patents of the selected drugs.

184. Peak Active Core Patent Count.

185. Peak Total Active Patent Count.

### A. A Tale of Two Thickets

Diving deeper into the alleged patent thickets reveals two types of relationships between different patents— (1) patents that are more inventive, and less prone to double patenting (patents that *do not* have claims overlapping with other patents); and (2) those that are less inventive and more prone to double patenting (patents that *do* have overlapping claims with other patents). This article argues that the accumulation of these two types of patents form the proposed two types of patent thickets. Figure 17-19 are visualizations that may assist in understanding the proposed concept.

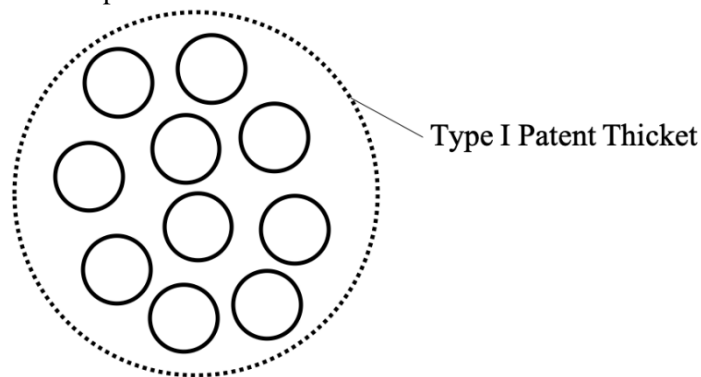


Figure 17: Visualization of A Hypothetical Type I Patent Thicket  
Source: own construction.

Figure 17 is a visualization of a hypothetical Type I Patent Thicket. The white circles each represent the scope of a patent that covers a particular aspect of the drug. Notice that the patent scopes do not overlap and are less prone to double patenting. When the number of these patents increase, they collectively amount to a Type I Patent Thicket (hereinafter, these patents will be termed as “Type I Patents” in this article). Figure 18 is a visualization of hypothetical Type II Patent Thickets. The shaded circles represent the scope of patents that cover a specific aspect of the drug. The patent scopes overlap in different degrees but do not overlap completely and are prone to double patenting. Each overlapping “cluster” amounts to one Type II Patent Thicket (hereinafter, these patents will be termed as “Type II Patents” in this article).



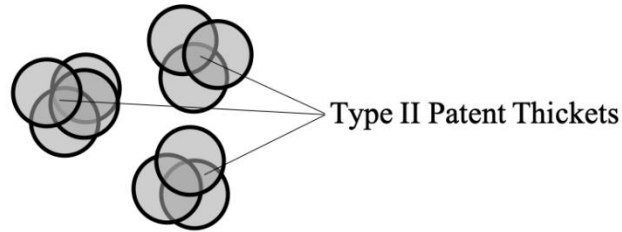


Figure 18: Visualization of Hypothetical Type II Patent Thickets

Source: own construction.

It would be unsurprising if a drug patent portfolio is a combination of the two types of patent thickets. Figure 19 illustrates this possibility. To avoid complication and interplay during Type I Patent Thicket assessments, each cluster of Type II patents is treated as “one single count.” That is, when assessing the number of patents in the alleged Type I Patent Thicket in Figure 19, the three Type II Patent Thickets are counted as three single counts, making a total of “nine patent counts” in the Type I Patent Thicket.

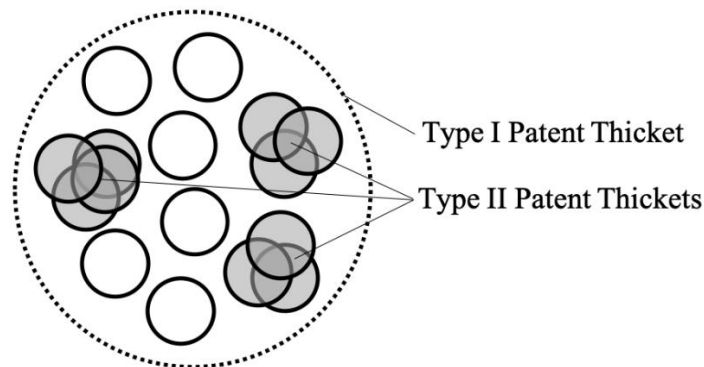


Figure 19: Visualization of Hypothetical Type I and Type II Patent Thickets

Source: own construction.

### *B. Assessment of Type I and Type II Patent Thickets*

Having the reasoning in mind, this Section first explains how the proposed method—using terminal disclaimers—can differentiate Type I Patents and Type II Patents. With the method at hand, this article moves on to assess the existence and extent of Type I and Type II Patent Thickets in the selected drugs. The results of the assessment are presented and

discussed in Sub-Section 2. Finally, to dive deeper into an alleged Type II Patent Thicket, a direct comparative analysis of one of Humira®'s alleged Type II Patent Thickets is conducted in Sub-Section 3.

### 1. Reasoning of assessment methodology

To determine whether Type I or Type II Patent Thickets exist, we must first be able to distinguish Type I Patents from Type II Patents. The most direct way to evaluate is, of course, to directly compare the patent claims with one another. This method is, however, tedious and time-consuming.

Fortunately, USPTO can help. Under statute, the act of obtaining overlapping patents is termed as “double patenting.”<sup>186</sup> There are two types of double patenting, (1) statutory-type double patenting; and (2) non-statutory-type double patenting (or obviousness-type double patenting).<sup>187</sup> The former is not allowed under 35 U.S.C. § 101, while the latter is allowed if the patents belong to the same patent owner and if such patent owner files a terminal disclaimer.<sup>188</sup>

Based on this fact, the article proposes that terminal disclaimers can indirectly identify whether patents overlap or whether they are prone to double patenting.<sup>189</sup> Patents that are tied together by terminal disclaimers can be deemed as Type II Patents; whereas the remaining patents can be considered as Type I Patents. Having this in mind, we would be able to further assess the extent of Type I and Type II Patent Thickets by counting the number of Type I and Type II Patents.

186. MPEP § 804 (9th ed. Rev. Jan. 2018).

187. JOHN GLADSTONE MILLS III ET AL., PATENT LAW BASICS § 15:50 (last updated Nov. 2018) (stating that “[t]hus, there are two types of double patenting: (1) the “same invention” type, which is based on 35 U.S.C.A. § 101; and (2) the “obviousness” type, which is judicially created doctrine based on public policy rather than statute and which is primarily intended to prevent prolongation of monopoly by prohibiting claims in a second patent not patentably distinguishing from claims in a first patent.”).

188. *See id.*; *see also* Sarkisian v. Winn-Proof Corp., 697 F.2d 1313, 1324–25 (9th Cir. 1983); Application of Vogel, 422 F.2d 438, 441–42 (C.C.P.A. 1970).

189. However, it must be stressed that the filing of a terminal disclaimer serves the only purpose to overcome an obviousness-type double patenting rejection and does not indicate that the patent owner admits to double patenting. *See* Ortho Pharm. Corp. v. Smith, 959 F.2d 936, 941 (Fed. Cir. 1992) (stating that “the filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting,” and does not mean that the patent applicant admitted to obviousness type double patenting). Nonetheless, this article argues that receiving an obviousness-type double patenting rejection or having the concern to receive such rejection so as to file a terminal disclaimer would be a more than sufficient indicator that the patents have overlapping claims or are prone to double patenting.

## 2. Results of Type I and Type II Patent Thicket assessment

By using the proposed method, this article assesses the core patents of the selected drugs.<sup>190</sup> The results are shown and discussed as follows.

Table 7 illustrates the counts of Type I and Type II Patents. Moreover, to present the distribution of the Type II Patents, the table also shows the number of Type II Patent Thickets and the average patent count in each Type II Patent Thicket.

Table 7: Counts of Type I and Type II Patents

Source: own calculation based on patents retrieved in empirical study.

<b>Brand Drug Name</b>	<b>Drug Category</b>	<b>Count of Type I Patents<sup>191</sup></b>	<b>Count of Type II Patents</b>	<b>Type II Patent Thicket Count<sup>192</sup></b>	<b>Average Type II Patent Count in Type II Thicket</b>
Rituxan®	Biologic	38	9	1	3.00
Humira®	Biologic	27	78	9	8.00
Revlimid®	Small-Molecule	10	26	5	4.40
Lyrica®	Small-Molecule	5	3	0	N/A
Enbrel®	Biologic	4	2	0	N/A
Eliquis®	Small-Molecule	3	0	0	N/A

According to the results in Table 7, it is interesting to see that the top-selling biologics have more Type I Patents compared to small-molecule drugs. However, when it comes to Type II Patents, this trend is less significant. We can interpret this result as top-selling biologics are more capable of forming Type I Patent Thickets compared to small-molecules;

190. The reason this article has chosen core patents to analyze is because that these are the patents that would most likely hinder biosimilar and small-molecule generic entry.

191. Type II Patent clusters are included and treated as one count.

192. Number of Type II Patent Thickets, wherein Type II Patent Thickets are defined as Type II Patent clusters that have three or more patents.

whereas top-selling biologics and small-molecules are both arguably capable of forming Type II Patent Thickets. Figure 20 may help to illustrate this. The x-axis is the count of Type I Patents, whereas the y-axis is the count of Type II Patents. Drugs situated on the right of the graph, such as Rituxan<sup>®</sup>, are more likely to form Type I Patent Thickets; and those located on the top of the graph, such as Revlimid<sup>®</sup>, are more likely to form Type II Patent Thickets. Noticeably, Humira<sup>®</sup> is situated on the right-top corner. This indicates that Humira<sup>®</sup>'s substantial number of patents not only are prone to overlap but also cover a great variety of aspects of the biologic.

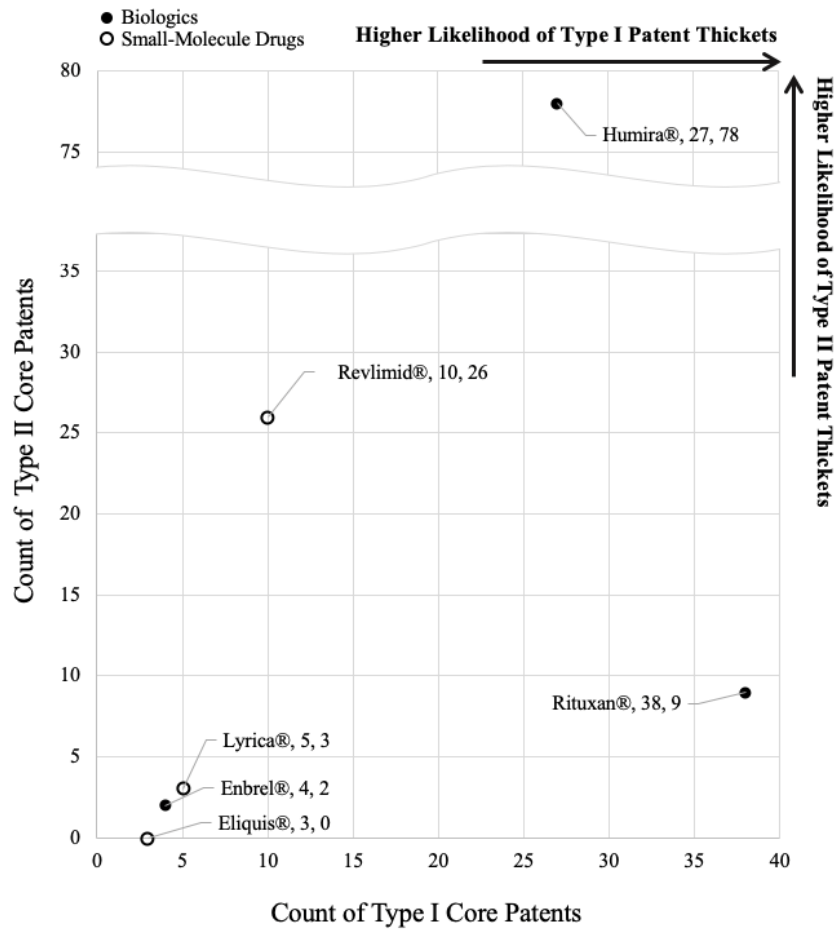


Figure 20: Type I Patent vs. Type II Patent Count Plot  
 Source: own construction based on patents retrieved in empirical study.

3. A Type II Patent Thicket example: direct claim comparison of AbbVie’s Humira® patents

As mentioned previously, the most straightforward way to identify Type II Patents is to dive directly into the patents and compare their claims. Since Humira® has the most tangled Type II Patent Thicket, this article selects Humira® as an example to conduct a claim comparison analysis.

The Type II Patent Thicket having the most patents is the “‘583 Type II Patent Thicket.” All of the patents in this Type II Patent Thicket are tied to U.S. Patent No. 8,216,583. There is a total of 21 patents in the ‘583 Type II Patent Thicket and all of these patents are core patents covering the formulation of Humira®. Interestingly, all of these patents also belong to the same patent family<sup>193</sup> and are all chained continuations of the same U.S. patent application.<sup>194</sup> They also have nearly identical patent specifications.

For illustration purposes, only claim one of the patents are compared. The components of claim one of each patent are broken down and compared with one another. Table 8 illustrates the comparison.

Table 8: Comparison of Claims 1 in the ‘583 Type II Patent Thicket  
Source: own construction based on patents retrieved in empirical study.

U.S. Patent No.	Components of the Formulation of Claim 1				
	Human TNF-α antibody <sup>195</sup>	Polyol	Polysorbate	Buffer System	Other

193. Family ID No. 31714885.

194. U.S. Patent Application No. 10/222,140 (filed Aug. 16, 2002) (now abandoned).

195. The original wording of all claims 1 of the patents in the ‘583 Type II Patent Thicket are identical or highly similar to “a human IgG1 anti-human Tumor Necrosis Factor alpha (TNF.alpha.) antibody, or an antigen-binding portion thereof . . .wherein the antibody comprises the light chain variable region and the heavy chain variable region of D2E7;” compare claim 1 of U.S. Patent No. 8,216,583, with claims 1 of U.S. Patent No.s 8,802,100, 8,802,101 8,802,102, 8,911,741, 8,916,157, 8,916,158, 8,932,591, 8,940,305, 9,114,166, 9,220,781, 9,272,041, 9,272,042, 9,289,497, 9,295,725, 9,302,011, 9,327,032, 9,732,152, 9,738,714, 9,750,808, 9,950,066; but for comparison purposes, these wordings are shortened as shown in Table 8. D2E7 is the original antibody name of adalimumab. See Joachim Kempeni, *Preliminary Results of Early Clinical Trials with the Fully Human Anti-TNFα Monoclonal Antibody D2E7*, 58 ANNALS OF THE RHEUMATIC DISEASES 170, 170-172 (1999).

8,216,583	20-150 mg/ml <sup>196</sup>	V <sup>197</sup>	X <sup>198</sup>	With Citrate or phosphate,	With surfactant
8,802,100	45-150 mg/ml	V	0.1-10mg/ml	at pH 4.5-7.0	N/A
8,802,101	45-105 mg/ml	V	0.1-10mg/ml	With acetate, at pH 4.5-7.0	N/A
8,802,102	45-105 mg/ml	V	0.1-10mg/ml	With succinate, at pH 4.5-7.0	N/A
8,911,741	20-150 mg/ml	V	V	With phosphate, at pH 4.0-8.0	N/A
8,916,157	20-150 mg/ml	X	X	at pH 4.0-8.0	With tonicity agent; surfactant
8,916,158	20-150 mg/ml	V	X	at pH 4.0-8.0	With surfactant

196. Instead of directly claiming the antibody D2E7, the patent claimed both the complementary determining region (hereinafter, CDR) amino acid sequences of D2E7's heavy and light chain and its possible amino acid substitution points. *See* U.S Patent No. 8,216,583, claim 2 (issued Jul. 10, 2012) (stating that the antibody claimed in claim 1 is D2E7).

197. "V" indicates that the patent limited its claim 1 to include the component. If the patent also specified other particular characteristics of the component, the characteristic will be listed in the table or in the footnote. *See, e.g., id.*

198. "X" indicates that the patent did not limit its claim 1 to include such component.

8,932,591	35-115 mg/ml <sup>199</sup>	V	X	With citrate and phosphate	With surfactant
8,940,305	20-150 mg/ml	V	X	With gluconate, at pH 4.0-8.0	With surfactant
9,114,166	50 mg/ml	X	X	V	N/A
9,220,781	50 mg/ml	V	V	With organic acid, at pH 4-8	N/A
9,272,041	50 mg/ml	V	V	With acetate, at pH 4-8	N/A
9,272,042	50 mg/ml	V	V	With phosphate, at pH 4-8	N/A
9,289,497	50 mg/ml	V	V	With gluconate, at pH 4-8	N/A
9,295,725	50 mg/ml	V	V	With succinate, at pH 4-8	N/A
9,302,011	50 mg/ml <sup>200</sup>	V	V	With organic acid, at pH 4-8	N/A

199. The claim did not directly claim the antibody D2E7 but claimed its CDRs. *See* U.S. Patent No. 8,932,591, claim 6 (issued Jan. 13, 2015) (stating that the antibody in claim 1 is D2E7).

200. Instead of claiming the antibody D2E7, the patent claimed the amino acid sequence of its heavy and light chain variable region.

9,327,032	50 mg/ml	V	V	With histidine, at pH 4-8	N/A
9,732,152	45-105 mg/ml	V	V	With histidine, at pH 4-8	N/A
9,738,714	45-105 mg/ml	V	V	With succinate, at pH 4-8	N/A
9,750,808	45-105 mg/ml	X	X	V	N/A
9,950,066	50 mg/ml	V	V	With citrate and phosphate	N/A

Comparison results in Table 8 show that most of the patents in the ‘583 Type II Patent Thicket all claim nearly identical components: a certain concentration of human TNF- $\alpha$  antibody, a polyol, a polysorbate, and a buffer system. The claim scopes of the patent members significantly overlap with one another. For instance, the scope of U.S. Patent No. 8,802,100 (hereinafter “the ‘100 patent”) overlaps with both U.S. Patents No. 8,802,101 (hereinafter, “the ‘101 patent”) and 8,802,102 (“the ‘102 patent”). The only difference is that the ‘100 patent does not further specify its buffer system, while the ‘101 patent and ‘102 patent do by limiting the buffer systems to include acetate and succinate respectively.<sup>201</sup>

Another example of overlapping claims in the ‘885 patent family would be U.S. Patents No. 9,220,781 (hereinafter “the ‘781 patent”) and 9,302,011 (hereinafter “the ‘011 patent”) wherein the only difference in claim 1 of the two patents is the “wording” of the claim describing the antibody. The ‘781 patent directly specifies the antibody to be D2E7 while

201. See, *supra* Table 8; U.S. Patent No. 8,802,100, claim 1 (issued Aug. 12, 2014); U.S. Patent No. 8,802,101, claim 1 (issued Aug. 12, 2014); and U.S. Patent No. 8,802,102, claim 1 (issued Aug. 12, 2014).



the '011 patent defines the antibody's heavy and light chain variable region to comprise a particular amino acid sequence.<sup>202</sup> However, comparing the claimed heavy and light chain sequences in claim 1 of the '011 with that of adalimumab (antibody DE27), showed that the sequences were actually identical.<sup>203</sup> There are also other overlapping claims in the '583 Type II Patent Thicket.<sup>204</sup> However, due to the extensiveness, the remaining claim overlaps in the '583 Type II Patent Thicket are not discussed further in this article. The chunky overlapping claims among the '583 Type II Patent Thicket also serves as an example that patents tied with terminal disclaimers do tend to double patent and have overlapping claims.

#### V. IMPACTS OF BIOLOGIC PATENT THICKETS: STACKING, STRETCHING AND SKYROCKETING

This article has so far demonstrated that patents cover biologics compared to small-molecule drugs. This indicates that among the top-selling drugs, biologics are more likely to form patent thickets in comparison to small-molecule drugs.<sup>205</sup> Dissecting the patent thickets into two types reveal while top-selling biologics and small-molecule drugs are both capable of large numbers of patents that amount to Type II Patent Thickets, only top-selling biologics are capable of forming high numbers Type I Patents that may accumulate to Type I Patent Thickets.<sup>206</sup>

This Part moves on to discuss the impacts of patent thickets and argues that patent thickets ultimately contribute to the skyrocketing of drug prices. The argument sets forth in three sections. Section A first discusses how patent thickets stack obstacles to patent challenges and force contenders into settlements. Next, Section B explains that patent thickets have the capacity to evergreen and that this capacity is contributed by the existence of Type I Patent Thickets by showing the correlation between the

202. U.S. Patent No. 9,220,781, claim 1 (issued Dec. 29, 2015) ("wherein the antibody is D2E7"); U.S. Patent No. 9,302,011, claim 1 (issued Apr. 5, 2016) ("wherein the antibody comprises a light chain variable region comprising the amino acid sequence of SEQ ID NO:1 and a heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 [emphasis added]").

203. Comparing the sequence listed in SEQ ID NO:1 and SEQ ID NO:2 of the '110 patent with adalimumab's light and heavy chain sequence respectively (DRUG BANK, *supra* note 144) using blastp suite-2sequences from BLAST@ (Blastp Suite-2sequences, U.S. NAT'L LIBRARY OF MED., NAT'L CTR. OF BIOTECH. INFO., <https://blast.ncbi.nlm.nih.gov/>) both yielded results of 100% identity with an E-value of 3e-80 for the former and 2e-89 for the latter. *Id.*

204. For example, the scope of claim 1 of U.S. Patent No. 9,732,152 covers entirely that of U.S. Patent No. 9,327,032; the '781 patent also covers the claim 1 of U.S. Patents No. 9,272,041, 9,272,042, 9,289,497, 9,295,725.

205. *See, supra* Part III.E.

206. *See, supra* Part IV.B.

number of Type I core patents with the total year span of the collective patent term. Finally, as Section C entails, the capability to force contenders into settlements and to evergreen may lead to the skyrocketing of drug prices.

#### *A. Type I and Type II Patent Thickets: Stacking Obstacles*

One of the most eminent capabilities of patent thickets is the leverage it provides for patent owners to force generics or biosimilar manufacturers into settlements. For example, *AbbVie* has brought all biosimilars referencing its blockbuster, Humira<sup>®</sup>, to the table, arguably with its patent thicket.<sup>207</sup> As of May 2019, all of the eight adalimumab (Humira<sup>®</sup>'s drug name) biosimilar companies, have given up to challenge its patent estate and agreed to enter into settlements with *AbbVie*.<sup>208</sup> Previously, *Boehringer Ingelheim* was the only biosimilar company willing to put up a fight for *AbbVie*'s Humira<sup>®</sup> U.S. market by raising an "unclean hands" defense, claiming that *AbbVie* formed a patent thicket to stake out competition.<sup>209</sup> However, after a two-year struggle, *Boehringer Ingelheim* eventually joined the settlement with its peers in the U.S. for an entry date set in 2023.<sup>210</sup>

There are at least three reasons patent thickets provide patent owners this power. First, the sheer number of patents increase the unpredictability of the litigation. The risk of losing litigation rises as the number of patents-in-suit increases.<sup>211</sup> According to a spokesperson from *Boehringer Ingelheim*, though the company wanted to make Cyltezo<sup>®</sup> [(*Boehringer Ingelheim*'s adalimumab biosimilar)] available earlier, due to "the unpredictability of litigation, the substantial costs of what would have been a long and complicated legal process and ongoing distraction to our business," the challenger surrendered and concluded that entering into the settlement was the best solution."<sup>212</sup> The patent owner would merely need one single patent claim to be valid and infringed to receive injunction relief, whereas generics or biosimilars would need to overcome layers of

207. Andrew Dunn, *With Boehringer Settlement, AbbVie Completes Humira Sweep*, BIOPHARMA DIVE (May 14, 2019), <https://www.biopharmadive.com/news/>.

208. *See id.*

209. *See id.*

210. Ben Hargreaves, *Boehringer Ends 'Distraction' by Signing Humira Biosimilar Deal*, BIOPHARMA-REPORTER (May 15, 2019), <https://www.biopharma-reporter.com/>.

211. Zachary Silbersher, *What Are the Lessons from Boehringer's Settlement with AbbVie Over Its Humira Biosimilar?*, MARKMAN ADVISORS (May 17, 2019), <https://www.markmanadvisors.com/>.

212. *See id.*

obstacles to achieve the freedom to operate.<sup>213</sup> This fact makes patent thickets able to provide “multiple patent lives” for the drug it covers and results in a lower possibility for the drug’s biosimilar or generic to be commercialized.

This result is an analogous manifestation of the “tragedy of the anti-commons” concept.<sup>214</sup> The concept describes the underuse of a certain resource due to there being too many owners holding the rights to exclude others from utilizing such resource.<sup>215</sup> In the present case, all core patents have the ability to block the commercialization of the drug. Similarly, as the number of core patents increases, the possibility to commercialize the drug decreases.

Second, consider costs. Even if we attempt to use the widely appraised lower-cost method—Inter Partes Reviews (hereinafter, IPR)—to cut down patent thickets, it would still be very costly, if at all feasible.<sup>216</sup> At its peak, *AbbVie* has 92 active core patents covering Humira®.<sup>217</sup> According to studies conducted by Patent Progress<sup>218</sup> and RPX<sup>219</sup>, the median cost to reach an IPR final decision is \$250,000. Thus, it would at least cost nearly \$23 million to invalidate all the patents, assuming that they are all, for some reason, unpatentable—which is often not the case.

Third, think of time. The mere existence of patent thickets increases the patent monitoring costs and time for biosimilars and small-molecule generics. Not to mention the time needed to spend on dissecting the patents if they are asserted.<sup>220</sup> If the plaintiffs provide an entry date earlier than a

213. See *BI's Amended Answers* at 63-64 (citing the words from *AbbVie* on “how events were playing out in adalimumab biosimilar litigation as it had desired: [‘W]hile the number [of patents found infringed] may not be 61, I’m confident the number is not going to be 0[.]’”).

214. Cf. Michael M. Heller, *The Tragedy of the Anticommons: Property in the Transition from Marx to Markets*, 111 HARV. L. REV. 621, 622-88 (1998).

215. See *id.*

216. See Josh Landau, *Inter Partes Review: Five Years, over \$2 Billion Saved*, PAT. PROGRESS (Sep. 14, 2017), <https://www.patentprogress.org/2017/09/14/inter-partes-review-saves-over-2-billion/> (stating that IPRs save more cost compared to litigations).

217. See, *supra* Part III.E.1.c. at Table 6.

218. See Landau, *supra* note 216.

219. *IPRs: Balancing Effectiveness vs. Cost*, RPX (2016), <https://www.rpxcorp.com/intelligence/blog/iprs-balancing-effectiveness-vs-cost/>.

220. There is, however, precedent where courts limit the number of patents or patent claims the patentee can assert in a lawsuit for the sake of judicial economy. In *re Katz Interactive Call Processing Patent Litigation*, 639 F.3d 1303, 1310-13 (Fed. Cir. 2011). Nonetheless, even if courts do impose a limit on the number of claims or patents assert-able, the process of determining how many and which patents and patent claims would still take up a great amount of time and cost if patent thickets are present.

court decision, biosimilar and small-molecule generic companies might just take the offer.<sup>221</sup>

Besides forcing settlements, patent thickets may also provide more bargaining power when negotiating settlement options with contenders.<sup>222</sup> For instance, *Amgen's Amgevita*<sup>®</sup> is granted the earliest U.S. entry date for adalimumab biosimilars, which is set to be at the end of January 2023;<sup>223</sup> as opposed to the European market where adalimumab biosimilar entry was already allowed in late 2018.<sup>224</sup> According to the Initiative for Medicines, Access & Knowledge (I-MAK)'s study, there are three times more patent applications covering *Humira*<sup>®</sup> in the U.S. compared to that in Europe.<sup>225</sup>

### *B. Type I Patent Thickets: Stretching Across Longer Year Spans*

Patent Thickets also have the capacity to evergreen. The Type I Patents contribute to this capacity as these patents would be able to have different expiration dates. Patents in Type II Patent Thickets, however, are tied to the same expiration date by terminal disclaimers and would thus not be able to evergreen.

Nevertheless, it should be stressed that patent evergreening should not be considered as a necessary consequence of Type I Patent Thickets. One can, on the same day, apply a considerable number of patents that cover different aspects of a drug. In this scenario, the patent owner allegedly formed a Type I Patent Thicket with no sign of evergreening. However, this usually never happens as ideas usually pop up gradually over time.<sup>226</sup> Indeed, a strong positive correlation exists between the count of Type I

221. See *BI's Amended Answers* at 63-64 (citing the words from *AbbVie* on "how events were playing out in adalimumab biosimilar litigation as it had desired: [\*]if Amgen were to prevail on every claim under 61 patents, the earliest we'll be getting a decision is 2020. . . we would then have obviously the right to appeal. That would take a year. And so that gets you into mid-2021. What's nice is you begin to see that the time line is starting to merge on that 2022 anyways, and I think the market is beginning to recognize that as well[.]")

222. See INITIATIVE FOR MED., ACCESS & KNOWLEDGE, *OVERPATENTED, OVERPRICED: SPECIAL HUMIRA EDITION* (2018), [http://www.i-mak.org/wp-content/uploads/2018/09/i-mak.humira.report.final\\_0917.pdf](http://www.i-mak.org/wp-content/uploads/2018/09/i-mak.humira.report.final_0917.pdf). (stating that "[s]ince AbbVie has not been as successful in aggressively evergreening its patent protection for Humira in Europe, competitors will enter the market considerably earlier in October 2018.").

223. See Dunn, *supra* note 207.

224. Andrew Dunn, *5<sup>th</sup> Humira Biosimilar Approved in EU as Market Entry Nears*, BIOPHARMA DIVE (Sep. 20, 2018), <https://www.biopharmadive.com/news/humira-biosimilar-europe-fifth-mylan-abbvie/532840/>.

225. See INITIATIVE FOR MED., ACCESS & KNOWLEDGE, *supra* note 222.

226. It is, however, considered an inequitable conduct to deliberately deceive the USPTO regarding material information or purposely conceal information upon applying a patent. See generally, *MILLS ET AL.*, *supra* note 187 § 15:50.

core patents and the length of accumulated core patent term (correlation coefficient = 0.95),<sup>227</sup> indicating that the more likely a Type I Patent Thicket is present, the longer the accumulated patent term is; and arguably the more likely evergreening exists.

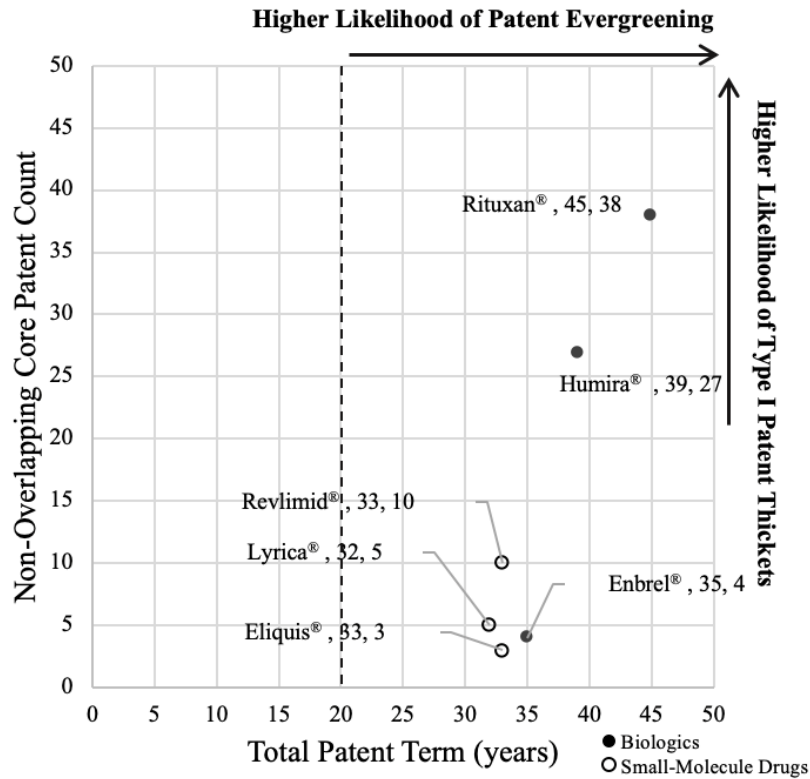


Figure 21: Core Patent Count vs. Patent Term Plot  
 Source: own construction based on patents retrieved in empirical study

C. Ultimate Impact: Skyrocketing Drug Prices

The idea behind establishing an expedited approval pathway for drugs is to lower drug prices through increased competition.<sup>228</sup> This theory

227. See, *infra* Figure 21.

228. See, *supra* Part II.C; see Andrew W. Mulcahy et al., *Biosimilar Cost Savings in the United States: Initial Experience and Future Potential*, 7 RAND HEALTH Q. 3 para. 9 (2018) (stating that “the

functions in practice if the generics and biosimilars reach the market. FDA's study on small-molecule drugs revealed that the market entry of generics is associated with the decrease of drug prices, with the second generic entry impacting prices the most.<sup>229</sup> As for top-selling biologics, Manova et. al's study showed that in the 18 European countries studied, the manufacturer price for etanercept and rituximab biosimilars are 36% and 39% lower than brand drug biologics respectively; whereas retail prices are each 11%, and 86% lower than their reference products.<sup>230</sup> With cheaper alternatives in the market, reference product sponsors respond by decreasing their drug prices, as can be seen from *Abbvie* offering an 80% discount for its blockbuster drug Humira<sup>®</sup> in face of biosimilar competition in the European tender markets.<sup>231</sup> The phenomenon of competition driving down drug prices can also be seen in the U.S.<sup>232</sup>

However, when it comes to the drugs that have monopoly status or are covered with a higher number of patents (arguably patent thickets), the pricing trends are not as friendly.<sup>233</sup> With biosimilars still off the U.S. market, Humira<sup>®</sup> prices in the U.S. have hiked by 6.2% in 2019 compared to the previous year despite inflation rate only around 2.4%.<sup>234</sup> In fact, the drug has increased more than 50% in price over the years, which can arguably be termed as "skyrocketing" considering the inflation rate was merely 11.6% in the same period.<sup>235</sup> The main reason these drug companies

rationale for a biosimilar approval pathway is to promote competition among manufacturers to lower prices and potentially increase access to medications.")

229. U.S. FOOD & DRUG ADMIN., *supra* note 102.

230. Manoela Manova, *Comparative Price Analysis of Biological Products for Treatment of Rheumatoid Arthritis*, 9 FRONT PHARMACOLOGY art. 1070 at 5.

231. Eric Sagonowsky, *AbbVie Offers Up 80% Humira Discount in EU Tender Market to Hold Off Biosimilars: Report*, FIERCE PHARMA (Oct. 31, 2018), <https://www.fiercepharma.com/>.

232. See, e.g., Ben Hirschler & Michael Shields, *Novartis Launches First U.S. 'Biosimilar' Drug at 15 Percent Discount*, REUTERS (Sep. 3, 2015), <https://www.reuters.com/>; *Biosimilars Launched in the US at a Significant Discount*, GENERICS AND BIOSIMILARS INITIATIVE, <http://www.gabionline.net/> (last updated Dec. 14, 2018) (stating that "US-based biosimilars specialist Coherus BioSciences (Coherus). . . would price its pegfilgrastim biosimilar at a 33% discount to the originator, Amgen's neutropenia treatment Neulasta (pegfilgrastim) and that "US pharma giant Pfizer. . . began shipping Retacrit to wholesalers at a list price of US\$11.03 per 1,000 units/mL, a 57% discount compared to Amgen's Procrit and a 33.5% discount compared to Johnson & Johnson's Epogen.").

233. See INITIATIVE FOR MED., ACCESS & KNOWLEDGE, *supra* note 42 (stating the drug price hikes of the drugs.)

234. See Michael Erman, *Drug Companies Greet 2019 with U.S. Price Hikes*, REUTERS, <https://www.reuters.com/> (last visited Jan. 3, 2019) (stating that the price of Humira<sup>®</sup> increased by 6.2%); *United States: Inflation rate from 1990 to 2018* (2019), STATISTA, <https://www.statista.com/statistics/191077/inflation-rate-in-the-usa-since-1990/> (last visited Nov. 9, 2019) (stating that the inflation rate in the U.S. is 2.4%).

235. See INITIATIVE FOR MED., ACCESS & KNOWLEDGE, *supra* note 227 (indicating that the price hike was 144% from 2012 to 2018), and since the drug increase was 6.2%, adding this to calculation

have the luxury to raise prices is arguably due to their market exclusivity.<sup>236</sup> The existence of patent thickets not only potentially prolongs this market exclusivity but also ensures that this market exclusivity would not be easily challenged.

Moreover, the absolute value of price elasticity of demand for pharmaceutical drugs is lower than 1, ranging from -0.18 to -0.60,<sup>237</sup> meaning that the need for drugs hardly depends on its price. This value makes sense because without these drugs, the patients' health conditions would be jeopardized. If drug prices are raised, the patients would rarely have the choice to opt out. However, not all patients can afford the increasing price of drugs.<sup>238</sup> The patent thicket problem is not only a matter of entry barriers for competitors but also a public health issue. There is arguably nothing wrong with a system that rewards innovation, but gaming the system to reap additional benefits at the expense of people's health and lives would be less intolerable.

## VI. CAUSES OF BIOLOGIC PATENT THICKETS

After covering the undesirable effects of patent thickets, this article moves on to discuss why patent thickets exist. Patent thickets are artificially established; thus, to answer the question—“why patent thickets exist,”—we need to consider the following two questions: (1) what motivates companies to file so many patents and (2) what allows companies to obtain these patents.

Section A covers the first question and shows that compared to small-molecule drugs, biologic companies have additional motives to file many patents. Section B answers the second question by pointing out that biologics have more patent subject matters that can be filed compared to small-molecule drugs. Section B also argues that while both small-molecule drugs and biologics are capable of forming Type II Patent Thickets, only biologics are capable of forming Type I Patent Thickets. Therefore, it is unsurprising that biologics are more likely to form patent thickets with larger extents.

yields an increase of 52.9% in the price of Humira®. See Erman, *supra* note 239. By multiplying the inflation rates from 2012 to 2018 yields an 11.6% increase. See STATISTA, *supra* note 239.

236. See Hakim, *supra* note 9.

237. Emily Cox, *Why Financial Incentives Aren't Enough to Move the Needle on Compliance*, 2 AM. HEALTH & DRUG BENEFITS 12, 12 (2009).

238. See generally, Sarah Jane Tribble, *Why the U.S. Remains the World's Most Expensive Market For 'Biologic' Drugs*, KAISER HEALTH NEWS (Dec. 20, 2018), <https://khn.org/news/u-s-market-for-biologic-drugs-is-most-expensive-in-the-world/>.

### A. Motivations to File (Many) Patents

Superficially, the first question— what motivates companies to file so many patents — can be easily answered: companies know that the effects of patent thickets can assist them in establishing a prolonged and hardly challengeable market exclusivity wherein they can set drug prices at will and retrieve the benefits on their investments.<sup>239</sup> However, besides then merely slapping the “greedy” label on drug companies—which admittedly may be true in some cases<sup>240</sup>—there is more to the story.

Another perspective is that companies may not be able to retrieve sufficient return on investment with a lower drug price as the current exclusivity term statute and regulations provide and guarantee. Although the statute provides a patent exclusivity term of 20 years,<sup>241</sup> due to the complicated approval process and the need to accumulate enough data to receive FDA approval, companies are unable to commercialize their investments in the first eight years of the patent term.<sup>242</sup> We can also see this phenomenon from the empirical study of this article: the average year between the first patent application to the market launch is approximately 8.17 years.<sup>243</sup> Even though the statute provides patent restoration, the additional five-year-term<sup>244</sup> may still not be enough for drug companies. Although for different purposes,<sup>245</sup> the five-year<sup>246</sup> and twelve-year<sup>247</sup> data

239. See generally, *infra* Part V.

240. Jeffrey Young & Shane Ferro, *Pharma Bro Emails Reveal Just How Greedy Drug Companies Can Be*, HUFFPOST (Feb. 2, 2016, last updated Dec. 19, 2016), [https://www.huffpost.com/entry/martin-shkreli-pharma-bro-drug-prices\\_n\\_56b0fac5e4b0655877f75453](https://www.huffpost.com/entry/martin-shkreli-pharma-bro-drug-prices_n_56b0fac5e4b0655877f75453).

241. 35 U.S.C. § 154(a)(2) (1952).

242. Matthew Herper, *Solving the Drug Patent Problem*, FORBES (May 2, 2002), <https://www.forbes.com/2002/05/02/0502patents.html#3be4544317bc> (stating that “patents protect drugs from copycat versions for 20 years after the drug is invented. This is a bitter pill for pharmaceutical companies because it can take eight years or more after invention to accumulate enough data to get a drug past the U.S. Food and Drug Administration.”).

243. The year span between each drug is as follows: Humira<sup>®</sup>: 6 years; Enbrel<sup>®</sup>: 3 years; Rituxan<sup>®</sup>: 9 years; Revlimid<sup>®</sup>: 9 years; Eliquis<sup>®</sup>: 13 years, Lyrica<sup>®</sup>: 9 years. See, *supra* Part III.E.2.b., at Figures 9-14.

244. 35 U.S.C. § 156(g)(6); see *Small Business Assistance: Frequently Asked Questions on the Patent Term Restoration Program*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/> (last visited Jun. 14, 2019).

245. It should be stressed that the purpose of data exclusivity is not to extend patent rights, nor to bar follow-on drugs to enter the market, but to prevent these follow-on drug companies from free-riding on the data collections of the new drug company; thus, necessitating them to either wait for the data exclusivity period to expire or to invest and conduct their own clinical trials for data collection. See KRISTINA M. LYBECKER, *THE BIOLOGICS REVOLUTION IN THE PRODUCTION OF DRUGS* 18 (2016), <https://www.fraserinstitute.org/>.

246. 21 U.S.C. § 355(c)(3)(E)(ii).

247. 42 U.S.C. § 262(k)(7)(A).



exclusivity provided by the Hatch-Waxman Act and the *BPCIA* would also not adequately compensate the loss of patent term since they usually overlap with each other.<sup>248</sup>

Even if the patent term is compensated, it is possible that the 20-year patent term itself is still insufficient. The development times for new protein therapeutics have increased steadily since the early 1980s, thus potentially increasing the erosion of patent term protection.<sup>249</sup>

Most importantly, patents can be challenged. If the only one patent is invalidated, the company would lose all of its exclusivity and have no guarantee that it will retrieve its investments. Filing more patents ensures that the exclusivity period is guaranteed and unchallenged.

Apart from the aforementioned motivations, biologic manufacturers have two additional incentives to file more patents compared to small-molecule companies. These incentives may be part of the reason why biologic patent thickets are more likely to be formed.

First, the time for new biologics to break-even and recoup their earlier investments is estimated to be about 12.9 to 16.2 years.<sup>250</sup> These extended break-even lifetimes mean that the 12-year data exclusivity period would be over just when, or even before, companies are about to gain profits. Thus, it would only be natural for companies to have the motivation to retrieve and maximize those gains after the 12-year data exclusivity period by filing a lot of patents.

Second, the unique nature of biologics may also have a role to play. Due to their larger size, and the existence of similar effective variants, it is relatively easier to invent around an existing biologic patent than that of small-molecule drugs.<sup>251</sup> As such, in terms of comprehensively covering the drug, the scope of a single biologic patent is relatively smaller compared to that of a small-molecule patent.<sup>252</sup> Given this, biologic companies have even more motivation to file more patents to compensate

248. See Henry Grabowski et al., *Data Exclusivity for Biologics*, 10 NATURE REVIEWS DRUG DISCOVERY 15, 16 (2011) (“[i]n those instances [where biologic patents provide relatively strong protection with significant patent life remaining at approval], the data exclusivity period has only a minimal effect on market exclusivity times and thus on health-care costs. The 12-year data exclusivity period therefore operates mainly as an ‘insurance policy’ to encourage innovation when patent protection is limited.”).

249. Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REV. DRUG DISCOVERY 479, 482 (2008). *But* this does not mean that it *will* erode the patent term, as companies may choose to file patents at later stages of the development.

250. See *id.* at 486.

251. LYBECKER, see *supra* note 245, at 17.

252. See *id.*

for the fact that one or a few patents will not fully cover the different “aspects” of the biologic.

### *B. What Makes Biologic Patent Thickets (More) Possible?*

Being motivated is one thing while being able to realize it is another. The existence of patent thickets also requires the possibility for it to form, not merely the motivations of the companies. When discussing the possibility for patent thickets to form, this Section refrains from covering the capability of companies as these internal factors are less relevant to the solution to patent thickets. Instead, this article focuses on what *external* factors allow the formation of patent thickets.

Sub-Section 1 first discusses how the ability to overcome obvious-type double patenting by filing terminal disclaimers allows the formation of Type II Patent Thickets and why it is a problem. Since this is an issue for patents in general, both small-molecule drugs and biologics are capable of forming Type II Patent Thickets. However, when it comes to Type I Patent Thickets, Sub-Section 2 argues that it is the nature of biologics and biosimilars that allows its formation.

#### 1. Type II Patent Thickets: Exploitation of Terminal Disclaimers

Many articles have proposed numerous insightful discussions regarding possible reasons why the USPTO grants more patents than the statutes allow, including the heavy workload for examiners;<sup>253</sup> the agency’s funding structure;<sup>254</sup> and examiners’ characteristics or competencies.<sup>255</sup>

253. See Saurabh Vishnubhakat & Arti K. Rai, *When Biopharma Meets Software: Bioinformatics at the Patent Office*, 29 HARV. J. L. & TECH 205, 211 (2015) (stating that “The USPTO operates under a number of institutional constraints that might cause application of existing patent law standards to be too lax. Perhaps most notably, examiners have a very limited amount of time to examine patents”); see generally Michael D. Frakes & Melissa F. Wasserman, *Is the Time Allocated to Review Patent Applications Inducing Examiners to Grant Invalid Patents?: Evidence from Micro-Level Application Data* (Nat’l Bureau of Econ. Res. Working Paper No. 20337, 2014), <http://www.nber.org/papers/w20337> [<http://perma.cc/BVC6-FG3R>] (finding evidence “demonstrating that such promotions [(of individual examiners that carry reductions in examination-time allocations)] are associated with reductions in examination scrutiny and increases in granting tendencies, as well as evidence that those additional patents being issued on the margin are of below-average quality”); John L. King, *Patent Examination Procedures and Patent Quality*, in PATENTS IN THE KNOWLEDGE-BASED ECONOMY 54 (Wesley M. Cohen & Stephen A. Merrill eds., 2003) (concluding that the examination hours and examination actions have remained largely consistent over time despite the increase of workload.).

254. See Michael D. Frakes & Melissa F. Wasserman, *Does Agency Funding Affect Decisionmaking?: An Empirical Assessment of the PTO’s Granting Patterns*, 66 VAND. L. REV. 67, 69-71, 84-85, 119 (2013) (stating that patents in categories with more maintenance fee received are more likely to be granted and that the agency was biased to allow patents that had higher renewal rates); see Arti K. Rai, *Growing Pains in the Administrative State: The Patent Office’s Troubled Quest for*

These factors may indirectly contribute to the formation of patent thickets but are not the central cause of the subject at hand.

The ability to overcome an obvious-type double patenting rejection by filing a terminal disclaimer is what allows patents castigated overlapping and non-inventive by critics<sup>256</sup> (Type II Patents) to exist. By filing multiple allegedly overlapping patents all tied with terminal disclaimers, drug companies accumulate Type II Patent Thickets.

The reason to allow obviousness-type double patenting overcome-able in the first place is that these patents mostly “involve a modification of or improvement upon what an inventor or his assignee has already patented. The desire is to be able to bring such improvement inventions within the protection of the patent system, at the same time giving an incentive for their disclosure.”<sup>257</sup>

However, two problems were recognized to arise if obvious-type double patenting were to be allowed: (1) patents that do not expire at the same time may extend patent terms, and (2) patents owned by different parties may give rise to troublesome litigation.<sup>258</sup> Thus, in hopes of solving the two problems, regulation requires patent owners to file a terminal disclaimer claiming that “the patent [(the patent that is deemed as obvious-type double patenting, or *the second patent*)] shall expire immediately if it ceases to be commonly owned with the other application or patent [(the

*Managerial Control*, 157 U. PA. L. REV. 2051, 2062 (2009) (stating that “the current fee structure also sets up an obvious financial incentive for the PTO to grant patents.”).

255. See Mark A. Lemley & Bhaven Sampat, *Examiner Characteristics and Patent Office Outcomes*, 94 REV. ECON & STAT. 817, 826 (arguing that “more experienced examiners cite less art, issue fewer initial rejections, and are more likely to grant patents,” while also excluding the possibility “that more senior examiners are more likely to grant could suggest that they can more quickly figure out what is patentable in an application” since “[t]he finding that more senior examiners systematically cite less prior art reinforces the inference that senior examiners are doing less work, rather than that they are merely getting it right more often than junior examiners); see also Shine Tu, *Invalidated Patents and Associated Patent Examiners*, 18 VAN. J. ENT. & TECH. L. 135, 165 (2015) (arguing that the main problem of granting invalid patents rise from the ability to find prior art. In particular, “77 percent of the prior art references used to invalidate patents were not found by the USPTO. . . [and] in cases where the invalidating prior art was a U.S. patent or U.S. patent application, the invalidating references were not found by the patent examiner 89 percent of the time.”).

256. See Kelly Davio, *Class Action Lawsuit Filed Against AbbVie and Biosimilar Developers Alleges Collusion*, THE CTR. FOR BIOSIMILARS (Mar. 19, 2019), <https://www.centerforbiosimilars.com/news/class-action-lawsuit-filed-against-abbvie-and-biosimilar-developers-alleges-collusion> (reporting that the complaints allege “AbbVie’s patent estate for Humira is [“]designed solely to insulate Humira from any biosimilar competition in the U.S. for years to come,[“] and that the company secured patents, many of them *overlapping and noninventive*” [emphasis added]).

257. In re Van Ornum, 686 F.2d 937, 948 (C.C.P.A. 1982); see P. J. Federico, Commentary on the New Patent Act, 35 USCA p. 49 (1954).

258. See MILLS, *supra* note 187.

application or patent that was cited as prior art for the obvious-type double patenting rejection, or *the first patent*)]” and that “*the second patent* application disclaims that part of the patent term that would extend beyond the expiration of *the first patent*.”<sup>259</sup>

Unfortunately, terminal disclaimers do not solve all the problems that obvious-type double patenting has to offer. Terminal disclaimers do not require patent applicants to link the validity or enforceability of the latter patent to that of the former.<sup>260</sup> This means that if the former patent is invalid, the latter patents bound to the former by terminal disclaimers are not indirectly invalid<sup>261</sup> or unenforceable.<sup>262</sup> Consequently, one cannot, after invalidating one of the many patents linked via terminal disclaimers, argue that the other patents linked with said terminal disclaimers are “indirectly” invalid.<sup>263</sup> Companies may have discovered this point and exploited it. The strategy would thus be to file a lot of alleged non-obvious

259. MILLS, *supra* note 187; see 37 C.F.R. § 1.321(b); MPEP § 804.02 (9th. Ed. Rev. 8.2017, Jan. 2018).

260. See MPEP §1490 at IV (9th. Ed. Rev. 8.2017, Jan. 2018) (stating that “[n]ote the exculpatory language in the second paragraph of the sample terminal disclaimer forms, PTO/SB/25. . . [t]hat language (referring to the language: “[i]n making the above disclaimer, the owner [*does not disclaim* the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term of any patent granted on said reference application, . . . in the event that: any such patent: granted on the pending reference application: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321. . . or is in any manner terminated prior to the expiration of its full statutory term as shortened by any terminal disclaimer filed prior to its grant.]”) is permissible.”).

261. See *Ortho Pharm. Corp.*, 959 F.2d at 941 (stating that “[i]n legal principle, the filing of a terminal disclaimer simply serves the statutory function of removing the rejection of double patenting, and raises neither presumption nor estoppel on the merits of the rejection” and does not mean that the patent applicant admitted to obviousness type double patenting by filing a terminal disclaimer); see also *SimpleAir, Inc. v. Google LLC*, 884 F.3d 1160, 1168 (Fed. Cir. 2018) (admitting that while “a terminal disclaimer is a strong clue that a patent examiner and, by concession, the applicant, thought the claims in the continuation lacked a patentable distinction over the parent” but agreeing with precedent that “[the] strong clue does not give rise to a presumption that a patent subject to a terminal disclaimer is patentably indistinct from its parent patents. It follows that a court may not presume that assertions of a parent patent and a terminally-disclaimed continuation patent against the same product constitute the same cause of action. Rather, the claim preclusion analysis requires comparing the patents’ claims along with other relevant transactional facts.”).

262. See *Pharmacia Corp. v. Par Pharm., Inc.*, 417 F.3d 1369, 1373-1375 (Fed. Cir. 2005) (admitting that although “terminal disclaimer ties the affected patents together; they expire on the same date and are enforceable only during periods in which they are owned by the same person. . . . Beyond their shared expiration date, however, *two disclaimed patents maintain significant attributes of individuality*,” and that patents bind by terminal disclaimers are independently presumed valid (emphasis added). Moreover, the Federal Circuit court also recognized the exculpatory language in the terminal disclaimer and states that “this language shows that the patentee justifiably expected individual treatment of the patents beyond their shared expiration date.” In conclusion, the Federal Circuit concluded that the terminal disclaimer alone did not bind the ‘368 patent and the ‘504 patent together for purposes of unenforceability due to inequitable conduct).

263. See *Ortho Pharm. Corp.*, 959 F.2d at 941.

patents all bound by terminal disclaimers to serve as multiple obstacles and “multiple lives” for invalidation.

Since this is an issue for patents in general, it is unsurprising that both small-molecule drugs and biologics are capable of forming Type II Patent Thickets as shown in the empirical research of this article.<sup>264</sup>

## 2. Type I Patent Thickets: Unique Nature of Biologics and Biosimilars

While both small-molecule and biologics are capable of forming Type II Patent Thickets, Type I Patent Thickets are arguably more possible to be formed by biologics. This is due to the nature of biologics. A biologic has significantly more “aspects”—manufacturing, in particular<sup>265</sup>—that can be covered by patents. To illustrate this, Figure 22 presents the number of core patents of the selected drugs by category.<sup>266</sup>

For the composition of matter patents, small-molecule drugs have the molecule itself and its polymorphs to be claimed; while for biologics, not only the protein itself, but also its variants and their properties can be claimed. For example, the composition of matter patents covering Revlimid<sup>®</sup> are only the molecule itself<sup>267</sup> and its polymorphs.<sup>268</sup> However, for the biologic Humira<sup>®</sup>, the patents not only include the monoclonal antibody<sup>269</sup> but also include a great variety of variants and the properties of the variants.<sup>270</sup>

Manufacture patents are what mostly make up the difference between biologics and small-molecule drugs. It is also this difference that allows biologic patent thickets, especially Type I Patent Thickets to be formed.<sup>271</sup>

264. Both the small-molecule drug Revlimid<sup>®</sup> and the biologic Humira<sup>®</sup> have filed a large number of terminal disclaimers and amounted to Type II Patent Thickets. *See, supra* Part IV.B.2.

265. *See, infra* Figure 22; *see* LYBECKER, *supra* note 245 at 17 (stating that “process patents are proportionally more important [in comparison to composition of matter patents].”).

266. The number of patents is calibrated to exclude the interplay of Type II Patent clusters: overlapping patents (or patents prone to double-patenting) tied by the same terminal disclaimer are collectively counted as “one patent.”

267. U.S. Patent No. 5,635,517, issued Jun. 3, 1997.

268. *See, e.g.*, U.S. Patent No. 7,465,800, issued Dec. 16, 2008; U.S. Patent No. 7,855,217, issued Dec. 21, 2010 (both claiming crystalline hemihydrate forms of the drug).

269. U.S. Patent No. 6,090,382, issued Jul. 18, 2000.

270. *See, e.g.*, U.S. Patent No. 9,255,143, issued Feb. 9, 2016 (claiming adalimumab having “more than 25% of the total N-linked oligosaccharides present”); U.S. Patent No. 9,505,833, issued Nov. 29, 2016 (claiming “methylglyoxal (MGO)-modified forms” of adalimumab); U.S. Patent No. 9,683,033, issued Jun. 20, 2017 (claiming a “composition compris[ing] less than 10% total acidic species of adalimumab”); U.S. Patent No. 9,085,618, issued Jul. 21, 2015 (claiming the properties of lysine variant species).

271. If we exclude the manufacturing patents of biologics, their number of patents will instantly be cut in half.

Among the selected drugs, only biologics have core manufacture patents,<sup>272</sup> with Rituxan<sup>®</sup> and Humira<sup>®</sup> having 31 and 27 core manufacture patents, respectively. This finding would not come as a surprise as the manufacture is the key to biologics.<sup>273</sup> The processes these patents claim include the general manufacture method of the drug;<sup>274</sup> general processes where a particular step is emphasized;<sup>275</sup> the purification of proteins;<sup>276</sup> the methods to control the expression or species of proteins;<sup>277</sup> and even ways to improve immunoglobulin productions.<sup>278</sup>

Formulations are also critical to biologics.<sup>279</sup> As such, patents that cover formulations are also an aspect that manufacturers can claim.<sup>280</sup> However, when it comes to treatment patents, the number can be more drug-specific than drug-type specific as the number of indications depends

272. A potential argument would be that the *Orange Book* does not allow the listing of process patents. See 21 CFR 314.53 (b)(1) (stating that “[p]rocess patents, patents claiming packaging, patents claiming metabolites, and patents claiming intermediates are not covered by this section, and information on these patents must not be submitted to FDA.”). The rebuttal to this argument is (1) core patents also include patents that were asserted in lawsuits (See *supra* Part III.C.4.), not only those listed on the *Orange Book*; and (2) even if conceding the fact that the manufacture patents of small-molecule drugs are not included in core patents, small-molecule drugs still have lower numbers of manufacturing patents when we include peripheral patents. The number of manufacturing patents (both core and peripheral patents included) of the small-molecule drugs Revlimid<sup>®</sup>, Eliquis<sup>®</sup>, and Lyrica<sup>®</sup> are 2, 0, and 10; while that of the biologics Humira<sup>®</sup>, Enbrel<sup>®</sup>, and Rituxan<sup>®</sup>, are 42, 27, and 41, respectively.

273. See, *supra* Part II.B.

274. See, e.g., U.S. Patent No. 8,163,522, issued Apr. 24, 2012 (claiming the general manufacturing process of etanercept, or Enbrel<sup>®</sup>); U.S. Patent No. 9,284,371, issued Mar. 15, 2016 (claiming the method of producing adalimumab, or Humira<sup>®</sup>).

275. See, e.g., U.S. Patent No. 9,234,032, issued Jan. 12, 2016 (claiming a fed-batch method to produce adalimumab with an emphasis on the conditions of the fed-batches.)

276. See, e.g., U.S. Patent No. 7,485,704, issued Feb. 3, 2009; U.S. Patent No. 8,231,876, issued Jul. 31, 2012.

277. See, e.g., U.S. Patent No. 9,062,106, issued Jun. 23, 2015 (claiming “A method for increasing the galactosylation level of a recombinantly expressed adalimumab”); U.S. Patent No. 9,150,645, issued Oct. 6, 2015 (claiming cell culture methods to reduce acidic species); U.S. Patent No. 9,234,033, issued Jan. 12, 2016 (claiming a method to control protein heterogeneity).

278. See, e.g., U.S. Patent No. 8,314,225, issued Nov. 20, 2012.

279. See Felicity Thomas, *Rising to the Challenge of Biologic Drug Formulation*, PHARMTECH (Mar. 2, 2019), <http://www.pharmtech.com/rising-challenge-biologic-drug-formulation> (stating that poorly formulated drugs may have significant impacts both on development, efficacy and patient safety— “[t]he drug must be thermally stable, possibly resistant to oxidation, and tolerate variations in light and other environmental stresses placed on it during manufacturing and packaging;” moreover, solubility must be assessed to ensure “that the formulation will result in high bioavailability without degrading or otherwise damaging the biologic itself.” Further challenges are also created “due to the varied nature and three-dimensional structure of different biologics”); see Sven Frokjaer & Daniel E. Otzen, *Protein Drug Stability: A Formulation Challenge*, 4 NATURE REVIEWS DRUG DISCOVERY 298 (2005).

280. For example, the formulation patents of Humira<sup>®</sup>. See, *supra* Part IV.B.3. at Table 8.

more on what drug it is than whether the drug is a biologic or a small-molecule drug.<sup>281</sup>

The number of core patents covering Revlimid<sup>®</sup> is quite interestingly high, given the fact that its small-molecule peers have fewer than ten core patents (Figure 22). This is because *Celgene* exploited the fact that Revlimid<sup>®</sup> requires FDA Risk Evaluation and Mitigation Strategies<sup>282</sup> approval.<sup>283</sup> According to the study, of the 29 core patents, 10 are patents directed to cover Revlimid's drug distribution system, amounting to the difference in patent counts compared to the other selected small-molecule drugs.<sup>284</sup>

As in the number of treatment patents, the difference in number of patents covering Revlimid<sup>®</sup> is a manifestation of the fact that the number of patents is also prone to be influenced by the nature of the drug itself and not just by whether the drug is a small-molecule or biologic. Along the same line of reasoning, the finding that the biologic Enbrel<sup>®</sup> has a relatively lower patent count compared to its biologic counterparts could probably be explained for similar reasons.<sup>285</sup> However, despite these factors, we still see

281. For example, as of May 28, 2019, the biologic Humira<sup>®</sup> has 10 indications. *See, Highlights of Prescribing Information*, U.S. FOOD & DRUG ADMIN at 1, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2018/125057s4091bl.pdf#page=1](https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s4091bl.pdf#page=1) (last visited Jun. 29, 2019). Both the small-molecule Revlimid<sup>®</sup> and the biologic Rituxan<sup>®</sup> has only 4 and 5 indications respectively. *See Highlights of Prescribing Information*, U.S. FOOD & DRUG ADMIN at 1, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/021880s0561bl.pdf#page=1](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021880s0561bl.pdf#page=1) (last visited Jun. 29, 2019); *Highlights of Prescribing Information*, U.S. FOOD & DRUG ADMIN at 1, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2019/103705s54541bl.pdf#page=1](https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/103705s54541bl.pdf#page=1) (last visited Jun. 29, 2019). This difference in the number of indications is reflected in the number of treatment patents. Humira has 28 treatment patents while both Rituxan<sup>®</sup> and Revlimid<sup>®</sup> only have 11.

282. Risk Evaluation and Mitigation Strategies, or REMS is “a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.” *Risk Evaluation and Mitigation Strategies (REMS)*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/> (last updated: Feb. 2, 2018).

283. *See* Alison Kodjak, *How a Drugmaker Gamed the System to Keep Generic Competition Away*, NPR (May 17, 2018), <https://www.npr.org/>.

284. By patenting the drug's distribution system, generics that seek to commercialize the drug would need to invalidate the patent or at least negotiate with *Celgene* to implement the drug distribution system, as FDA requires generics to use the same REMS as branded companies. *See id.* *But see Statement from FDA Commissioner Scott Gottlieb, M.D., On New Policies to Reduce the Ability of Brand Drug Makers to Use REMS Programs As a Way to Block Timely Generic Drug Entry, Helping Promote Competition and Access*, U.S. FOOD & DRUG ADMIN. (May 31, 2018), <https://www.fda.gov/> (stating that FDA may consider waiving the requirement of generics to implement the same REMS as the branded drug company). Another way brand companies can restrict competition by exploiting the REMS programs is to refuse to sell generic companies' drugs when generics need at least 5,000 doses of the brand drug to run bioequivalence and bioavailability studies. The “reasoning” behind this refusal to deal is to argue that this violates their REMS regulation. *See id.*

285. For example, Enbrel<sup>®</sup> is a fusion protein. Unlike Humira<sup>®</sup> and Rituxan<sup>®</sup>, which are monoclonal antibodies, the manufacture process of fusion proteins does not involve antibody production. *See* Cynthia A. Challener, *Fusion Proteins Pose Manufacturability Challenges*, 30

the general trend that biologics are more *capable of* and more *prone to* forming Type I Patent Thickets compared to small-molecules.

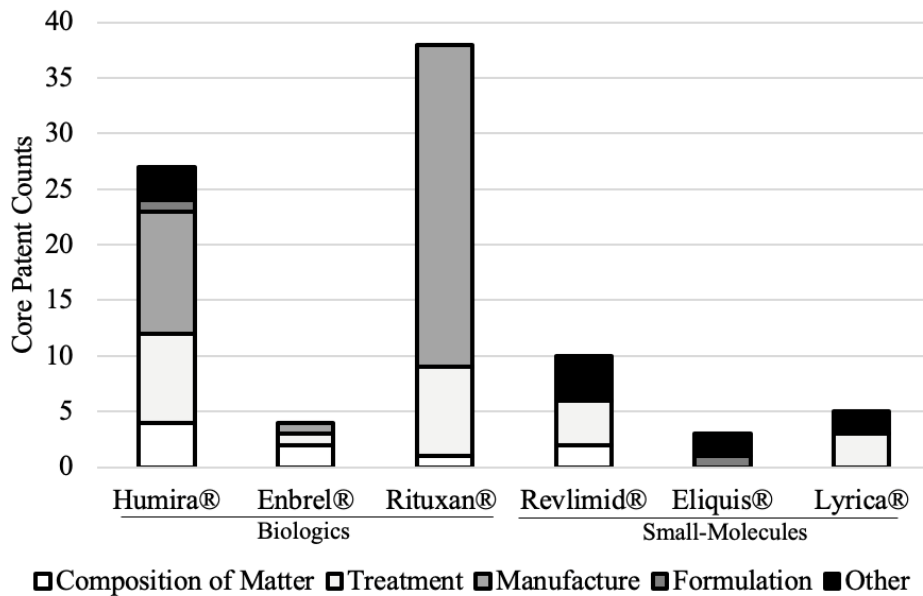


Figure 22: Calibrated Core Patents Counts by Category<sup>286</sup>  
 Source: own construction based on patents retrieved in empirical study.

The other reason that Type I Patent Thickets exist is biosimilars simply being bio-“*similar*.” Being “similar” allows the possibility to be different from the reference biologic product,<sup>287</sup> meaning that there can be patents that do not claim the reference biologic product itself but are potential threats to the entry for biosimilars.<sup>288</sup> These patents are rightfully considered as part of the patent thicket—since they hinder biosimilar

BIOPHARM INT’L 30-31, 37 (2017); see Lucas Silva Carvalho et al., *Production Processes for Monoclonal Antibodies*, INTECHOPEN (Feb. 8, 2017), <https://www.intechopen.com/>. This difference in manufacturing processes may partially explain the differences in the number of manufacturing patents between these biologics.

286. For comparison purposes, patents that claims different categories in the same patent, for example those that claim both the composition of matter and the manufacture thereof, are categorized in the “others” group.

287. See U.S. FOOD & DRUG ADMIN., *supra* note 57.

288. See, e.g., *BI’s Amended Answers* at 64 (stating that the asserted patents do not cover the reference product); see *supra* note 169.



entry—and are not unlawful being in the hands of reference product sponsors even though they do not claim the reference product itself.<sup>289</sup> In fact, the existence of these patents merely indicates that the reference product sponsors are playing the patent game very well.<sup>290</sup> The issue that patent owners do not exercise the inventions in their patents has always existed in the patent system and is entirely legal and even rewarding under our patent system.<sup>291</sup>

This problem has not surfaced, or at least not magnified, for small-molecule drugs because there is no such thing as being “similar” for small-molecule drugs. Small-molecule generic drugs are required to be bio-“equivalent.”<sup>292</sup> Therefore, small-molecule generic manufacturers would only need to worry about the patents that cover the brand name small-molecule drug. But for biosimilars manufacturers, they have to hack through or scrutinize not only the patents claiming the reference biologic product itself, but also patents that claim its variations. With this in mind, interchangeability status may shed some light on circumventing these Type I Patent Thickets; since theoretically, achieving interchangeability would indicate higher biosimilarity, and the patents that need to be hacked through would consequently decrease.<sup>293</sup>

## VII. SOLUTIONS TO THE BIOLOGIC PATENT THICKET PROBLEM

With the orchestrations of patent thickets and its potential problematic consequences in mind, a discussion on possible solutions to the patent thicket problem is needed.

289. 35 U.S.C. § 154 (stating that a grant to the patentee “the right to *exclude* others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States, and, if the invention is a process, of the right to *exclude* others from using, offering for sale or selling throughout the United States, or importing into the United States, products made by that process, referring to the specification for the particulars thereof.” Nowhere does it require nor provide the right for the patentee to exercise the invention claimed).

290. They are playing well in that they file patents that claim what their potential competitors would manufacture. The “best players” in the patent systems are those that file patents that claim what potential competitors may commercialize. Patent Trolls—entities that “[do] not make or sell a particular item or service, but who [seek] to enforce patent rights against alleged infringers in an attempt to collect licensing fees”—is a good demonstration of this concept. BUS. L. INC., CORP. COUNSEL’S GUIDE TO INTEL. PROP. § 1:47 (2018 ed.).

291. See Nick Statt, *Apple Ordered to Pay Patent Troll More Than \$500 Million in iMessage Case*, THE VERGE (Apr. 10, 2018), <https://www.theverge.com/>. But see, Lauren Cohen et al., *The Growing Problem of Patent Trolling*, 352 SCI. 521, 521-522 (2016) (condemning the problem of patent trolls).

292. See Bagley, *supra* note 48.

293. See, *infra*, Part VII.B.2.

In this Part, Section A first discusses why a comprehensive optimal solution to the patent thicket problem is not easily obtainable. Section B then covers how a current proposal raised by legislators would help increase the transparency of the problem. Section B also proposes that transparency can be increased by demanding interchangeability patent listing. Next, Section C explains how antitrust may serve as an *ex post* regulation by deeming the act of using patent thickets to restrain competition unlawful. Finally, Section D presents *ex ante* regulation proposals that may aid in alleviating the patent thicket problem.

### A. A Thorny Issue to Tackle

Before discussing the solutions, this Section explains why biologic patent thickets is a thorny issue to tackle. First, as Sub-Section 1 argues, whether a patent thicket exists is challenging to identify. Second, though patent thickets have problematic consequences, Sub-Section 2 argues that the laws that allow them to exist in the first place are not without merits. There are justifiable reasons why the patents in these patent thickets exist. Thus, it is crucial that we do not throw the baby out with the bathwater when attempting to solve the patent thicket problem. Third, it would be tough to prove patent thickets unlawful by relying on patent litigation defenses. Moreover, even if there exist applicable patent defenses, the defendant, or biosimilar companies, would have to stay and fight through the litigation. However, as Sub-Section 4 covers, due to the misaligned interests with patients, biosimilar companies are unlikely to persist in the lawsuit.

#### 1. Definition

The very first challenge is the definition issue. It is difficult to draw a clear-cut line as to how many patents amount to a patent thicket.<sup>294</sup> Admittedly, this article merely uses relative patent counts to assess the existence of Type I and Type II Patent Thickets without assigning absolute

294. See Memorandum and Order Concerning Doc. No. 71 at \*4 n.3, AbbVie Inc. et al v. Boehringer Ingelheim International GmbH et al, CIVIL No. 17-1065-MSG-RL (D. Del. Jun. 4, 2018) (No. 112), <https://casetext.com/> (hereinafter, “*Memorandum*”) (citing that “the boundary line [of patent thickets] between licit and illicit conduct might be, is not clear.”).

cut-values.<sup>295</sup> It is relatively harder to solve the problem if there can be times when we are unsure whether the problem exists.<sup>296</sup>

## 2. Babies and bathwater

Although both Type I and Type II Patent Thickets have problematic consequences, such as increased monitoring, transaction and litigation costs of biosimilar manufacturers and thus the delay of their market entries,<sup>297</sup> the primary purposes of the laws that allow the formation of patent thickets are not without merits. Continuously granting patently distinct inventions in different patents provides innovation incentives;<sup>298</sup> while allowing obvious-type double patenting rejections to be overcome-able by filing terminal disclaimers encourages inventors to disclose incremental improvements of their already-patented inventions.<sup>299</sup> Even though its negative impacts are real, it is critical that we do not throw the baby out with the bathwater when we attempt to deal with these impacts. We should not sacrifice the benefits provided by these laws for the sole reason of ridding patent thickets or its undesirable effects. However, to achieve a sweet spot where innovation is rewarding but at an acceptable cost of public interest is anything but simple.

## 3. Patent defenses are impractical

Given the fact that the patents granted in the alleged Type I and Type II Patent Thickets are not entirely without merits and that the line of what accumulates to a patent thicket is unclear, courts may be reluctant to accept the act of amassing and asserting a purported large number of patents being unlawful.<sup>300</sup>

295. *See, supra* Part IV.B.2.; *see also, supra* note 192.

296. *But see* Affordable Prescriptions for Patients Act of 2019, S.1416, 116th Cong. § 27 (a)(11) (2019) (a bill introduced attempting to define what patent thicketing is rather the absolute number of patents that would qualify as a patent thicket).

297. *See, supra* Part V.

298. *See* ROBERT A. MATTHEWS, JR., 1 ANNOTATED PATENT DIGEST § 1:2 (updated: Jun, 2019). Granting patents to newly patently distinct inventions encourages continuous innovation; and when the patents expire, the inventions are contributed to the public. *See* *Aronson v. Quick Point Pencil Co.*, 440 U.S. 257, 262 (1979). If patently distinct follow-on inventions were instead consolidated into the first patent, inventors would have less incentive to disclose follow-on inventions or to improve patented inventions.

299. *In re Van Ornum*, 686 F.2d at 948; *see* P. J. Federico, *supra* note 257; *see, supra* Part VI.B.1.

300. *See Memorandum* at \*4 n.3 (stating “[w]hether the creation of a ‘patent thicket’ can amount to a cognizable defense to a claim of patent infringement.”).

Nonetheless, *Boehringer Ingelheim* attempted to argue that such act is unlawful by raising the “unclean hands defense<sup>301</sup>” against *AbbVie* when *AbbVie* promised the enforcement of its “patent estate.” The unclean hands defense “is an equitable defense in which the defendant argues that the plaintiff is not entitled to relief on account of the fact that the plaintiff is acting unethically or has acted in bad faith with respect to the subject of the complaint.”<sup>302</sup> In mounting this defense, *Boehringer Ingelheim* is essentially accusing that the alleged “wrongful” patent thicket is causing the launch delay of *Boehringer Ingelheim*’s biosimilar.<sup>303</sup> However, it is unclear “[w]hether the creation of a “patent thicket” can amount to a cognizable defense to a claim of patent infringement.”<sup>304</sup> After all, as courts acknowledge, “[t]he simple act of applying for and receiving a patent, standing alone, can hardly be the basis for patent invalidation.”<sup>305</sup>

Other traditional patent defenses may also be unfeasible or impractical for patent thickets. For example, patent misuse defense would be unsuccessful, because theoretically, the patent owner has not “impermissibly broaden the scope of the patent grant.”<sup>306</sup>

#### 4. Misaligned interests

Even if the unclean hands defense is applicable, to succeed in this defense, the defendant bears the burden to prove that the cause of its biosimilar launch delay resulted from the alleged patent thicket.<sup>307</sup> The nature of this defense paradoxically tilts biosimilar manufacturers to settle rather than to stay and fight. To prove biosimilar launch delays, the

301. See *BI’s Amended Answers* at 39 (stating that “[p]laintiffs cannot obtain relief, including injunctive relief, because of their unclean hands.”); see also *id.* at 74 (stating that “Plaintiffs’ efforts to create a patent thicket or estate in the United States are part of a global effort to improperly delay competition with respect to adalimumab”); see Silbersher, *supra* note 122 (stating that “[*Boehringer Ingelheim*]’s defense is very unique. . . [and] is essentially untested.”).

302. LAWRENCE M. SUNG & JEFF E. SCHWARTZ, PATENT LAW HANDBOOK § 5:7 (2018-2019 ed.).

303. See *BI’s Amended Answers* at 40.

304. See *Memorandum* at \*4 n.3.

305. *Id.*

306. SUNG & SCHWARTZ, *supra* note 302 at § 5:6 (stating that “[t]he policy of the patent misuse doctrine is to prevent a patentee from using the patent to obtain market benefit beyond that which inures in the statutory patent right. (*Monsanto Co. v. McFarling*, 363 F.3d 1336, 1341, 70 U.S.P.Q.2d 1481, 2004-1 Trade Cas. (CCH) ¶ 74358 (Fed. Cir. 2004) (quoting *Mallinckrodt, Inc. v. Medipart, Inc.*, 976 F.2d 700, 704, 24 U.S.P.Q.2d 1173 (Fed. Cir. 1992) (abrogated by, *Impression Products, Inc. v. Lexmark Intern., Inc.*, 137 S. Ct. 1523, 198 L. Ed. 2d 1, 122 U.S.P.Q.2d 1605 (2017))). . . in the cases in which the restriction is reasonably within the patent grant, the patent misuse defense can never succeed.”).

307. *Id.* at § 5:7 (“[t]he defendant bears the burden of proving by clear and convincing evidence that the plaintiff acted with unclean hands.”).

biosimilar launching plans, a typically “highly confidential and tightly guarded information,”<sup>308</sup> are likely to be the subject of discovery.<sup>309</sup> The eventual settlement between *AbbVie* and *Boehringer Ingelheim* demonstrates perfectly well that the interests of patients and biosimilar manufacturers are misaligned.<sup>310</sup>

A system that relies on the entry of biosimilars to drive down biologic prices rests on the assumption that the patients and biosimilar manufacturers are aligned. The patent thickets exploit the fact that they are not.<sup>311</sup>

### B. Increasing Transparency

Regardless of what methods are chosen to solve the patent thicket problem, transparency will always be a critical component. Without transparency, legislators and the public would have little idea of what is happening. This Section acknowledges the current legislative effort—the proposed Purple Book Continuity Act of 2019—while delineating out points that may warrant improvement.

#### 1. Purple Book Continuity Act of 2019

Recently passed House on May 8th, 2019, the Purple Book Continuity Act of 2019<sup>312</sup> aims to increase the transparency of the patent dance by requiring reference product sponsors to publicize the exchange list codified in 42 U.S.C. 262 (k)(1)(3)(A).<sup>313</sup> However, unlike small-molecule drugs,<sup>314</sup> the timing of patent listing in the *Purple Continuity Act* is set at no later

308. Zachary Silbersher, *Is Boehringer Ingelheim Planning to Launch Its Humira Biosimilar At Risk?*, MARKMAN ADVISORS (Dec. 13, 2018), <https://www.markmanadvisors.com/>.

309. For example, in *AbbVie Inc. et al v. Boehringer Ingelheim International GMBH et al*, CIVIL No. 17-1065-MSG-RL (D. Del. filed Aug. 2, 2017), the plaintiff, *AbbVie*, had successfully persuaded the court to compel the discovery of the defendant, *Boehringer Ingelheim's* biosimilar launch plans. See Memorandum concerning Plaintiff's Motion for more Complete Interrogatory Answers at 9, *AbbVie Inc. et al v. Boehringer Ingelheim International GMBH et al*, CIVIL No. 17-1065-MSG-RL (D. Del. Feb. 22, 2019) (No. 234), <https://docs.justia.com/cases/federal/district-courts/delaware/dedce/1:2017cv01065/62839/428>.

310. *See id.*

311. Silbersher, *supra* note 211.

312. Purple Book Continuity Act of 2019, H.R.1520, 116th Cong. (2019), hereinafter as “*Purple Book Continuity Act*.”

313. *See id.* at § 2 (stating that “the reference product sponsor shall provide such list of patents [(list of patents under subsection (1)(3)(A))] (or supplement thereto) and their corresponding expiry dates to the Secretary, and the Secretary shall, in revisions made under clause (ii), include such information for such biological product . . .”).

314. Patent information must be submitted along with the New Drug Application. *See* 21 CFR 314.53(b)(1).

than 30 days after reference sponsors provide the patent list codified in 42 U.S.C. 262 (k)(1)(3)(A). This timing is when the patent dance music has just begun, rather when reference product sponsors first file their Biologic License Applications.<sup>315</sup>

If this version of bill becomes law, biosimilar manufacturers would undoubtedly benefit by being able to narrow down on what patents reference product sponsors would likely assert and by being less vulnerable to the abuse of reference product sponsors listing irrelevant patents on the patent list.

However, the extent of these benefits is limited. First, the publication of patent information is set only after the engagement of the first biosimilar applicant. Thus, only following biosimilar applicants will benefit from this amendment. Therefore, without providing additional incentives, biosimilar applicants may be discouraged to become the first to engage in the patent dance.<sup>316</sup> Second, consider the nature of biosimilars. As explained previously, patents that block one particular biosimilar may not inevitably hinder the entry of another.<sup>317</sup> Thus, even if biosimilar manufacturers learn what patents other applicants were asserted against, the knowledge may not necessarily apply to themselves. Biosimilar applicants may still have to conduct a scrutinized patent search and analysis themselves.

## 2. Interchangeability patent listing

As a method to address the aforementioned limitations in the *Purple Book Continuity Act*, this article proposes adding “interchangeability patent listing.” Congress can mandate biologic companies to disclose patents that they believe can reasonably assert against applicants whose biosimilars have achieved interchangeable status when filing their biologics licenses applications. This requirement would provide an earlier publication of patents that do cover the reference product itself, which in theory, would

315. *Purple Book Continuity Act* § 2 (“Not later than 30 days after a list of patents under subsection (l)(3)(A), or a supplement to such list under subsection (l)(7), has been provided by the reference product sponsor to the subsection (k) applicant respecting a biological product included on the list published under this subparagraph, the reference product sponsor shall provide such list of patents . . .”).

316. Note that no incentive is provided to the first biosimilar applicant. *See generally*, 42 U.S.C. § 262. Only the first applicant that achieves interchangeability is entitled a one-year-exclusivity. 42 U.S.C. § 262(k)(6).

317. *See, supra* Part III.C.4.

most likely be the patents that all manufacturers of biosimilars, including those with and without interchangeability, need to hack through.<sup>318</sup>

### C. Ex Post Regulations

The solution does not stop here. Increasing transparency does not change the fact that there would still be many patents, nor does it help biosimilar manufacturers circumvent the effects of these alleged patent thickets. This Section discusses how *ex post* regulation, antitrust in particular, may disincentivize companies from forming Type I and Type II Patent Thickets by deeming the act of deliberately restricting competition by amassing a large number of patents unlawful.

Sub-section 1 first points out current ongoing antitrust lawsuits against the alleged formation of *AbbVie's* patent thicket and its purportedly improper use as a means to illegally restrain trade. This article argues that antitrust litigations by consumers may currently be the most feasible way to address patent thickets. However, with the many obstacles to overcome, the lawsuit would not be an easy battle for the plaintiffs. In particular, this article argues that under the current antitrust regime, plaintiffs need to argue that the present patent thicket is more of a Type II Patent Thicket as opposed to a Type I Patent Thicket to prevail.

To make things easier, Congress can codify the act of using patent thickets to restrain competition as illegal. As such, a bill was introduced recently by the Senate to target patent thickets directly. Sub-section 2 turns to discuss what the bill entails and how it would potentially solve some of the thorny problems patent thickets present if it does make it into law. The bill targets not only Type II Patent Thickets but also Type I Patent Thickets without severely sacrificing the merits patents in the Type I Patent Thicket may provide.

#### 1. Antitrust litigation: *In re: Humira (Adalimumab)* Antitrust Litigation<sup>319</sup> as the example

*AbbVie's* patent strategy has drawn publicity, criticism and legal attention alike, with several organizations accusing its patent thicket of

318. This conclusion relies on the assumption that the reference product and interchangeable biosimilar are more similar in general compared to biosimilars that cannot achieve interchangeable status. However, note that interchangeability is defined in terms of clinical efficacy and safety rather than equivalence. See 42 U.S.C. §§ 262(k)(4)(A)(ii), (B).

319. *In re: Humira (Adalimumab) Antitrust Litigation*, CIVIL No.1:19-cv-01873 (N.D. Ill., consolidated Jun. 4, 2019), hereinafter "*In re: Humira Antitrust Litigation*."

being anticompetitive.<sup>320</sup> Along with several pay-for-delay class actions, the lawsuits were consolidated into *In re: Humira (Adalimumab) Antitrust Litigation*.<sup>321</sup> The class actions have accused *AbbVie* of the following three wrongdoings: (1) illegitimate accumulation of more than 100 patents covering *Humira*<sup>®</sup>; (2) improper deals for delaying competition until 2023 in the U.S.; and (3) anticompetitive agreement in allowing *Amgen* earlier entry than biosimilar manufacturers in the U.S.<sup>322</sup>

Antitrust litigation may currently be the most feasible way to combat patent thickets. First, the plaintiffs of the class action suits are consumers, rather than biosimilar manufacturers, they are more likely to stay and fight the battle.<sup>323</sup> Second, the act of using patent thickets to maintain monopoly status have a slight chance to fall in what Sherman Act § 2 and what the Court's leading decision, *United States v. Grinnell Corp.*<sup>324</sup> defines and articulates as “the offense of actual monopolization.” However, it should be emphasized that there are controversial issues in this argument. This article will not ambitiously conclude that courts *will* find patent thickets anticompetitive or by doing so eliminate the patent thicket problem. Instead, this article intends to identify the potential challenging issues plaintiffs may face in the present antitrust litigation and to opine on how such issues could be argued to reach a more fruitful result.

Sherman Act § 2 does not delineate the specific elements of the offense of actual monopolization as it only states that it is illegal for anyone to “monopolize. . .any part of the trade or commerce among the several States, or with foreign nations.”<sup>325</sup> Therefore, the Supreme Court has outlined the two elements that constitutes offense of actual monopoly under Sherman Act § 2: “(1) the possession of monopoly power in the relevant market and (2) the willful acquisition or maintenance of that power as distinguished from growth or development as a consequence of a superior product, business acumen, or historic accident.”<sup>326</sup>

320. Eric Sagonowsky, *AbbVie's Humira Antitrust Woes Snowball as Class-Action Plaintiffs Pile In*, FIERCEPHARMA (Apr. 3, 2019), <https://www.fiercepharma.com/>.

321. *In re: Humira Antitrust Litigation*, No. 93, (N.D. Ill. Jun. 4, 2019).

322. Jeff Overley, *Meet the Top Attorneys in AbbVie's Antitrust Battle Royal*, LAW360 (Jun. 7, 2019), <https://www.law360.com/articles/1145098/meet-the-top-attys-in-abbvie-s-antitrust-battle-royal>.

323. Silbersher, *supra* note 211.

324. *U.S. v. Grinnell Corp.*, 384 U.S. 563, 570–571 (1966).

325. 15 U.S.C. § 2; *see* WILLIAM C. HOLMES & MELISSA MANGIARACINA, ANTITRUST LAW HANDBOOK § 3:3 (2018-2019 ed.).

326. *See id.*; *see also Grinnell Corp.*, 384 U.S. at 563, 570–571; *Verizon Communications Inc. v. Law Offices of Curtis V. Trinko, LLP*, 540 U.S. 398, 124 (2004) (“It is settled law that [the] offense [of monopolization] requires, in addition to the possession of monopoly power in the relevant market, ‘the



The first element would be relatively easy to demonstrate. To do so, plaintiffs would need to first identify the relevant product and the geographic dimensions of the market,<sup>327</sup> and then show proof that “the defendant possesses [‘monopoly power’] within the relevant market.”<sup>328</sup> The relevant product is adalimumab, including Humira<sup>®</sup> and its biosimilars; and the geographic area is the United States. *AbbVie*’s monopoly power can be shown by stating that *AbbVie* has 100% of the sales share in the relevant product and market during the given period and presenting the fact that other biosimilars or biologics are not interchangeable with Humira<sup>®</sup>.<sup>329</sup>

The second element is the hard part. Plaintiffs have to demonstrate that *AbbVie* willfully acquired or maintained its monopoly power, “as distinguished from growth or development as a consequence of a superior product, business acumen, or historic accident.”<sup>330</sup> This element is difficult to establish as courts have been reluctant to penalize monopolists that engage in normal competitive behavior that is allowed to smaller competing firms solely because the monopolist is dominant.<sup>331</sup> The issue at stake would thus be whether filing a massive number of patents and vigorously asserting them constitutes an unlawful act. If *AbbVie* believes that the patent suits are not without merit, which *AbbVie* would no doubt vigorously defend, courts would probably side with *AbbVie*.<sup>332</sup> Moreover, the act of being litigious does not constitute a sham as long as there were “plausible argument[s] in the suit] on which [patent owners] could have prevailed.”<sup>333</sup>

However, courts have held that monopolists that tend to further establish their monopoly position to restrict competition rather than for legitimate business purposes violate Sherman Act § 2 even when the

willful acquisition or maintenance of that power as distinguished from growth or development as a consequence of a superior product, business acumen, or historic accident.”).

327. *Standard Oil Co. of New Jersey v. U.S.*, 221 U.S. 1, 61 (1911).

328. *See HOLMES & MANGIARACINA, supra* note 330, § 3:4.

329. *See id.*

330. *Grinnell Corp.*, 384 U.S. at 570–571.

331. *See HOLMES & MANGIARACINA, supra* note 326.

332. *C.f. Professional Real Estate Investors, Inc. v. Columbia Pictures Industries, Inc.*, 508 U.S. 49, 50 (1993) (filing a copyright infringement suit against plaintiff is not an act of monopolization where defendant had probable cause to believe the action is not without merit. To be held as a sham, a two-tier test must be satisfied: “First, the lawsuit must be objectively baseless in the sense that no reasonable litigant could realistically expect success on the merits;” and second, “whether the baseless suit conceals ‘an attempt to interfere directly’ with a competitor’s business relationships.”).

333. *Kaiser Found. Health Plan, Inc. v. Abbott Labs., Inc.*, 552 F.3d 1033, 1046 (9th Cir. 2009).

defendant's conduct is not otherwise illegal.<sup>334</sup> Unfortunately, none of these precedents show that the act of monopolists asserting a sheer amount of presumed valid and enforceable patents violates Sherman Act § 2.<sup>335</sup> The plaintiffs in *In re: Humira Antitrust Litigation* would probably have a better chance in proving the second element by emphasizing that the patents covering Humira<sup>®</sup> are overlapping, non-inventive, or perhaps even obtained through fraudulent conduct, if possible. That is, they should argue that the Humira<sup>®</sup> patent thicket is more of a Type II rather than a Type I Patent Thicket. However, from the study of this article, we know that the Humira<sup>®</sup> patent thicket may be more of a combination of both types of patent thickets.<sup>336</sup>

In sum, for *In re: Humira Antitrust Litigation*, the court would have to answer at least the following three questions to arrive at a conclusion that Humira<sup>®</sup>'s patent thicket is anticompetitive: (1) whether the act of monopolists obtaining Type I Patent Thickets and using them to block competition is anticompetitive; (2) whether the act of monopolists obtaining Type II Patent Thickets and using them to block competition is anticompetitive; and if the court finds opposite answers to the former two questions, (3) whether or to what extent does each of the two former acts taint the other to render the "entire act of patent thicketing" a violation of Sherman Act § 2.<sup>337</sup> These questions are also the very hurdles the plaintiffs in the present case are facing.

334. See HOLMES & MANGIARACINA, *supra* note 325. ("For example, illegal monopolizing conduct has been found in . . . a monopolist's exploitation of a fraudulently procured patent or otherwise sham litigation to drive competitors from the market; [See *Walker Process Equipment, Inc. v. Food Machinery & Chemical Corp.*, 382 U.S. 172, 177; see also *In re Lipitor Antitrust Litigation*, 868 F.3d 231, 270 (2018) (reversing a dismissal of a "Walker Process" claim in which the defendant fraudulently procured a patent and subsequently used it to restrict competition.)] and in extreme instances of tortious misconduct, fraud, and other exclusionary acts used to entrench the defendant's monopoly position without any plausible procompetitive explanation. [See *Xechem, Inc. v. Bristol-Myers Squibb Co.*, 372 F.3d 899, 901 (7th Cir. 2004) (stating that the district court erred in dismissing a claim that accused the defendant of filing false patents to the FDA and by exploiting FDA laws, stymied generic competition. In the reversal, the court specifically stated that "[e]xclusionary patent-related practices that violate the antitrust laws are valid claims.")].

335. See *id.*

336. The patents in Type I Patent Thickets are arguably patently distinct and should be independently presumed valid and enforceable.

337. Note that the third question is only fair for patent owners since not all patents in the patent thicket are created equal. Treating different patents unitedly as one would be irresponsible if the third question was not answered persuasively. However, there is precedent that different patent claims are treated unitedly as in inequitable conducts, which may serve as a cross-reference in the present lawsuit. See *Kingsdown Med. Consultants, Ltd. v. Hollister, Inc.*, 863 F.2d 867, 877 (Fed.Cir.1988) ("When a court has finally determined that inequitable conduct occurred in relation to one or more claims during prosecution of the patent application, the entire patent is rendered unenforceable.") Nevertheless, these precedents do not expand across the borders of different patents (See *Pharmacia Corp.*, 417 F.3d at 1375

## 2. Affordable Prescriptions for Patients Act of 2019

To make it easier for courts to decide on the anticompetitive effect of patent thickets, Congress can codify the act of “patent thicketing” as anticompetitive into law. As such, introduced in the Senate on May 9th, 2019, the Affordable Prescriptions for Patients Act of 2019<sup>338</sup> is the only bill introduced that attempts to target patent thickets directly so far.<sup>339</sup> Moreover, the bill also aims to give the Federal Trade Commission more strength on this matter.<sup>340</sup>

The *Affordable Prescription for Patients Act* characterizes the act of using patent thickets to restrict competition as “patent thicketing”:

“an action taken to limit competition by a patentee with respect to a drug approved. . .in which (i)\_(I) the patentee obtains patents in the same patent family . . . (aa) that claim the drug or biological product. . .and (bb) whose effective filing date does not precede the date of filing the application [for New Drug Application or Biologic License Application]. . .; or (II) the underlying composition of matter patent is found invalid and the patentee obtains patents in the same patent family or patent portfolio that claim [other aspects of] the drug or biological product. . .; (ii) an abbreviated new drug application referencing such approved drug or a biosimilar biological product license application referencing such licensed biological product could not be marketed without practicing one or more of the inventions claimed in the additional patents described [herein]; and (iii) the Commission determines that the patentee improperly limited competition by obtaining patents described [herein.]”<sup>341</sup>

The bill also provides additional factors the Federal Trade Commission can consider when determining whether patent thicketing exists, including whether (1) the additional patents stem from few patent families; (2) the additional patents have common specifications; (3) the additional patents did not issue on an application that underwent restriction;

(stating that the case law that inequitable conduct occurring in one or more claims during prosecution of patent application, “however, applies only to claims in *one* patent.”)), and it would be up to the court of this case to determine whether the purportedly wrongdoing of Type II Patent Thickets would infect the presumably legal Type I Patent Thickets.

338. Affordable Prescriptions for Patients Act of 2019, S.1416, 116th Cong. (2019), hereinafter “*Affordable Prescriptions for Patients Act*.”

339. See *Affordable Prescriptions for Patients Act* § 27.

340. *Affordable Prescriptions for Patients Act* (stating that the purpose of the Act is “[t]o amend the Federal Trade Commission Act to prohibit anticompetitive behaviors” such as patent thicketing and product hopping).

341. *Affordable Prescriptions for Patients Act* § 27(a)(11)(A).

(4) the additional patents have overlapping or identical claims; (5) the additional patents have been granted to the patentee on formulations or compositions of the product and not used; (6) one or more of the additional patents have been invalidated in an inter partes review and others.<sup>342</sup>

In general, the bill delineates a decently comprehensive definition for patent thicketing. Notice that the definition of patent thicketing also includes patents that belong in the Type I Patent Thicket.<sup>343</sup> Nevertheless, the bill does not entirely sacrifice the merits of these patents as it provides a chance to argue on rebuttal that the alleged patent thicket is pro-competitive.<sup>344</sup>

#### *D. Ex Ante Regulations*

Though having the ability to disincentivize companies from forming patent thickets, antitrust is an *ex post* regulation; meaning that intervention does not come into play until biosimilar manufacturers or consumers are purportedly harmed, or at least when the Federal Trade Commission finds out the establishment of a patent thicket. Moreover, attempting to solve the patent thicket problem with more litigation may lock up biosimilar manufacturers in lengthy legal battles and ultimately delay biosimilar market entry. It would be more desirable if patent thickets were not allowed to form or to have such a significant effect in the first place. This Section presents two proposals that would help in achieving this ideal.

Sub-Section 1 proposes a small tweak the USPTO can implement to alleviate the effects of Type II Patent Thickets without compromising the incentive of incremental improvement disclosure obvious-type double patenting can provide. Sub-Section 2 proposes a more transformative reform that targets Type I and Type II Patent Thickets collectively. Named as the “All-in-One” approach, the reform aims to consolidate all patents and exclusivities into a single, more flexible, and perhaps a longer exclusivity period. This reform would thus streamline the system and make the exclusivity periods more predictable. While additional details warrant discussion, this proposal may nevertheless serve as a reference for further research.

342. *See id.* at § 27(a)(11)(B).

343. *See Affordable Prescriptions for Patients Act* § 27(a)(11)(A)(i)(II).

344. *Affordable Prescriptions for Patients Act* § 27(b)(1)(B).

### 1. Targeting Type II Patent Thickets: the election of patents

Terminal disclaimers have not comprehensively covered the problem that obviousness-type double patenting provides patents multiple “lives.”<sup>345</sup> However, the courts’ reasoning to not tie the validity and enforceability of patents with terminal disclaimers is not without merits. By treating the patents unitarily would run against what is provided under 35 U.S.C. § 282:

“[e]ach claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim.”<sup>346</sup>

Thus, to alleviate the effects of Type II Patent Thickets without running afoul of 35 U.S.C. § 282, this article suggests that in addition to the current requirements in the terminal disclaimer,<sup>347</sup> the USPTO demands patent owners to disclaim that only one patent in the patent group tied with terminal disclaimers be enforceable against each alleged infringer regarding the same alleged infringing product. The selection of the patent is up to the patent owner. Different patents can be asserted against different alleged infringers; but for each alleged infringer, the number of enforceable patents in the patents tied with terminal disclaimers is one. If the alleged infringer manages to invalidate the elected patent, the patent owner would not have a second chance to file other patents that are tied with the same terminal disclaimer against the same alleged infringer.

Doing so would solve the problems that come from Type II Patent Thickets without mechanistically tying the validity and enforceability of the patents. This proposal is in line with the purpose of allowing obvious-type double patenting to be overcome in the first place. The system was initially designed to protect incremental improvements of the patented invention,<sup>348</sup> rather than allowing patent owners to amass large numbers of patents vigorously and to assert them all aggressively. Limiting the enforceability of the patents to the one patent plaintiffs believe would

345. The validity and enforceability are not tied by terminal disclaimers. *See Ortho Pharm. Corp.*, 959 F.2d at 941; *Pharmacia Corp., Inc.*, 417 F.3d at 1373-1375). Therefore, one cannot, by invalidating or proving that a patent is unenforceable, indirectly invalidate or deem another patent tied by terminal disclaimers to the former patent unenforceable; thus, making the patent having “multiple lives.” *See, supra* Part VI.B.1.

346. 35 U.S.C. § 282(a); *see Ortho Pharm. Corp.*, 959 F.2d at 942.

347. *See MILLS ET AL.*, *supra* note 187; *see* 37 C.F.R. § 1.321(b); USPTO, MPEP § 804.02 (9<sup>th</sup> Ed. Rev. 8.2017, Jan. 2018).

348. *See In re Van Ornum*, 686 F.2d 937, 948 (C.C.P.A. 1982); *see* P. J. Federico, Commentary on the New Patent Act, 75 J. PAT. & TRADEMARK OFF. SOC’Y 161, 208 (1993); *see, supra* Part VI.B.2.

obtain the most fruitful results will not strip away this benefit. On the other hand, it would also effectively neutralize the negative effects of Type II Patent Thickets. Competitors would only need to deal with “a single version” of the invention instead of multiple patents claiming incremental improvements of the same invention.

Moreover, the proposal can also be indirectly backed by courts as there is precedent where courts impose a limit on the number of patents or patent claims the plaintiff can assert in a litigation for simplicity.<sup>349</sup> Though following the same line of reasoning, the present proposal is better than the district court’s discretion in that it avoids the complications of deciding the number of patents that the plaintiff can assert when considering patents tied with terminal disclaimers.

## 2. Targeting Type I and Type II Patent Thickets collectively: the “All-in-One” approach

Admittedly, electing patents would only serve as an *ex ante* regulation for Type II Patent Thickets. Type I Patent Thickets, though justifiable in some aspects,<sup>350</sup> would still exist and complicate litigations. As explained below, the “All-in-One” approach aims to prevent the downsides of Type I and Type II Patent Thickets collectively without completely sacrificing the merits the patents that amount to the thickets bring. The proposal does so by consolidating all drug patents and exclusivities into one longer, but transparent and flexible exclusivity period.

Under the proposed system, the current expedited pathway would still exist. The main difference is how the exclusivity periods are granted. Upon filing a New Drug Application of Biologics License Application, applicants would be required to disclaim that once the applied drug is approved, patents covering the drugs would all be unenforceable against future aNDA (abbreviated New Drug Application) or aBLA (abbreviated Biologic License Application) applicants—similar to terminal disclaimers. This disclaimer will force all brand drugs to go onboard the proposed system. Moreover, drug companies will also be required to disclose all relevant information regarding the drug, including the manufacture and the method of use of the drug—arguably to an extent similar to the disclosure in patents. In return, the law will guarantee a certain period of exclusivity

349. In re Katz Interactive Call Processing Patent Litigation, 639 F.3d at 1303 (ruling that the district court did not violate the plaintiff’s due process rights in the complex litigation involving when the district court demanded the plaintiff to limit the number of asserted claims against the defendant).

350. See, *supra* Part VII.A.2.; see *supra* note 298.

wherein such period no generics or biosimilar approvals will be granted by the FDA. Under this regime, companies can rest assured that they will be guaranteed to see a return on their investments. The length of the exclusivity period, however, can be adjusted according to their development costs.

To incentivize improvements, the system allows drug companies to submit and disclose drug improvements to the FDA. If FDA finds the improvements warranted—similarly to the non-obvious standard in patents—the drug companies could be prized with an extended “bonus” exclusivity period. However, a maximum limit of the total exclusivity term must be set. On the other hand, if companies fail to properly disclose their inventions, the FDA, either acting on its own or with from the request of challengers, could penalize drug companies by deducting time from their exclusivity periods. Once the exclusivity period ends, generics or biosimilars would be able to enter the market. In cases where patents were later acquired after the submission of new drug or biologics license applications, laws can mandate that only reasonable remedies be available.

In sum, the proposed system has the following benefits. First, all patents and exclusivities would be consolidated into one. This prevents the complexity Type I and Type II Patent Thickets would give rise to, including the increased monitoring costs and opaqueness of patents and exclusivities. Second, a guaranteed, more secured and perhaps longer but flexible exclusivity period would provide brand drug companies an insurance to receive a return on their investments; and thus incentivizing them to lower their drug prices.<sup>351</sup> The flexibility of the exclusivity period also reflects the fact that not all drugs are created equal and would thus deserve different lengths of exclusivity periods.<sup>352</sup> Fourth, by granting bonus exclusivity periods, improvements of the drug could be incentivized, thereby maintaining the benefits<sup>353</sup> patents provide. The upper length limit of the exclusivity period balances the interest of generic and biosimilar

351. Under the current patent system, drug companies may try to retrieve their investments as soon as possible by raising drug prices because they are in fear of losing their patent exclusivity; since patents can be challenged and invalidated. *See, supra* Part VI.A. However, if the exclusivity period is guaranteed and longer, drug companies would be less inclined to retrieve their investments in such a short period. Drug prices would arguably be lower.

352. The current drug system acknowledges this fact by granting additional exclusivities periods to different types of drugs. For example, “[t]he first sponsor of a designated orphan drug to obtain FDA marketing approval for the designated rare disease or condition receives seven years of marketing exclusivity.” *FDA at Rare Disease Day / February 28, 2011*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/> (last updated: Nov. 3, 2017).

353. *See, supra* Part VII.A.2.; *see, supra* note 298.

manufacturers by providing them a precise timeline as to when they are guaranteed to enter the market. Under this regime, the bonus periods are not ever-extending, therefore neutralizing the possibility of evergreening. Fifth, the system discloses the inventions to the public. Once the exclusivity period ends, the public is free to use the invention. Sixth, only one agency—the FDA— is responsible for granting the exclusivities. The USPTO does not participate. This simplifies matters as exclusivity information such as patent information does not need to rely on the timely and properly listing of drug companies. Seventh, the system provides an adjustable penalty for those not complying. In the event of non-disclosure, the FDA, either acting on its own or with from the request of challengers, could penalize drug companies by deducting their exclusivity period. As opposed to all-or-none exclusivity protection, as in the current patent system, an adjustable penalty would balance the interests of these brand drug companies.

However, it should be noted that the “All-in-One” approach may only be suitable for the pharmaceutical industry. This is because unlike other industries, drugs must undergo examination before reaching the market. The required examination provides the opportunity to consolidate the exclusivities into one. Should industries that do not have this examination process characteristic encounter patent thicket issues, the presented approach would be of limited use.

Furthermore, the “All-in-One” approach is not without problems. It is a system with flexible exclusivity period lengths. This leads to the questions: who should have the power to decide the length of the exclusivity period for each type of drug and how should that agency handle this task. Moreover, what available remedies exist if drug companies do not agree with the agency’s decision? How about biosimilar or generic companies; do they have a say in this decision? Not to mention: what kinds of improvements would be qualified to receive the bonus exclusivity periods? How long would those bonus periods be? Additionally, what would happen if a company’s non-compliance with the system is found only after the exclusivity periods are over? Furthermore, how do we ensure that the companies timely and properly disclose their inventions?

Some of these questions are not unique. For example, the question of “how do we ensure that the companies timely and properly disclose their inventions?” is not an unforeseen issue. Under the current patent system, it is considered inequitable conduct to deliberately deceive the USPTO regarding material information upon applying for a patent. If inequitable



conduct is found, the patent would be held unenforceable.<sup>354</sup> The analogous penalty under the proposed system could be a deduction from the exclusivity period. Other issues, on the other hand, are new challenges the proposed system presents. In order to fully implement this system, at least the questions discussed above warrant thorough discussion.

### VIII. CONCLUSION

This article demonstrates that among the top-selling drugs, biologics obtain more patents compared to small-molecule drugs and are thus arguably more likely to form patent thickets. With an in-depth analysis of the alleged patent thickets, this article argues that there are two types of patent thickets: (1) Type I Patent Thickets, which are amounted by patents that are inventive and less prone to double patenting; and (2) Type II Patent Thickets, which are accumulated by patents that are less inventive and more prone to double patenting. Though both types of patent thickets complicate patent litigation, stave away contenders and indirectly result in high drug prices, only Type I Patent Thickets have the capability to evergreen.

While both small-molecules and biologics are capable of forming Type II Patent Thickets, only biologics are capable of forming Type I Patent Thickets. This is because Type I Patent Thickets are a result of the interplay between the unique nature of biologics and biosimilars; while Type II Patent Thickets are due to the utilization of terminal disclaimers.

Even though Type I and Type II Patents are not completely without merits, the negative impacts of patent thickets are real. Thus, to alleviate these impacts without sacrificing the benefits these patents provide, this article discusses possible solutions to solve the problem. Antitrust litigations and current legislative proposals may serve as *ex post* regulations for the patent thicket problem. However, it would be more desirable if patent thickets are prevented in the first place. As such, two proposals are presented: the first being a minor tweak the USPTO can implement to target Type II Patent Thickets, and the second being a more transformative proposal that consolidates the drug patents and exclusivities into one.

The patent thicket is a complicated issue with the interests of multiple stakeholders involved. Before reaching a definite conclusion on how to solve this problem, more discussions and debates are warranted. This

354. See generally, MILLS ET AL., *supra* note 187, § 15:50.

article sheds some light on this heated topic in the hopes of contributing to these discussions and serving as a reference for future legal reforms or adjustments.