Minnesota Journal of Law, Science & Technology

Volume 17 | Issue 2 Article 10

6-2016

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Note

Decline of Dosage Regimen Patents in Light of Emerging Next-Generation DNA Sequencing Technology and Possible Strategic Responses

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The successful launch of a pharmaceutical product requires an investment of billions of dollars and carries significant risks, mostly due to the complexity of pharmaceutical sciences, intricacy of the regulatory scheme, intensive competition, high marketing cost, and the continuing change of intellectual property law.[1] To obtain returns sufficient to recoup their investments and fund further research, pharmaceutical companies place great focus on devising and pivoting strategies to strengthen and extend their rights of exclusivity.[2] One chief practice is to build a strong patent portfolio, keeping competitors at bay and ensuring an advantageous position when litigation arises.[3] A carefully managed patent strategy provides protection not only to the chemical composition of the drug, but also to new developments and improvements of the

* J.D. Candidate, 2017, University of Minnesota Law School. The author greatly appreciates the guidance and support from Professor Christopher Frank and the excellent work from editors and staff members of the *Minnesota Journal of Law, Science & Technology*.

1. Jason Millman, *Does it Really Cost $2.6 Billion to Develop a New Drug?*, WASH. POST (Nov. 18, 2014), https://www.washingtonpost.com/news/wonk/wp/2014/11/18/does-it-really-cost-2-6-billion-to-develop-a-new-drug/.

2. Carolyne Hathaway, John Manthei & Cassie Scherer, *Exclusivity Strategies in the United States and European Union*, UPDATE, May/June 2009, at 34, https://www.lw.com/upload/pubcontent/_pdf/pub2655_1.pdf.

3. Brenda Herschbach Jarrell & William B. Asher, *Lifecycle Management: Patent Prosecution Strategies in Pharmaceutical and Biotechnology Cases*, CHOATE HALL & STEWART LLP (2007), https://www.choate.com/uploads/113/doc/lifecycle-management-patent-prosecution-strategies.pdf.

basic compound.[4] These "follow-on" patents may bring significant values to their owners in both defensive and offensive postures.[5] In addition to strengthening, or even extending the terms of, these patents, careful management of the secondary patents "can minimize the risk of being blocked by competitors' second generation patents" and being "prevented from practicing certain embodiments" within their basic composition patent.[6]

Patents directed to dosage regimens of a drug are one important example of these follow-on improvements.[7] Dosage regimens relate to the modality of drug administration, including formulation, route of administration, drug dose, dosing interval, and treatment duration.[8] These dosage decisions are made "to maximize a desired set of responses and minimize an undesired set of responses."[9] Part of the clinical trial for new chemical entities involves verifying dosage regimens to evaluate their therapeutic value as per Food and Drug Administration (FDA) request.[10] However, determining the appropriate dosage regimen for a drug is particularly difficult, because patients' responses to drugs are multifactorial, multigenetic, and coupled with low treatment adhesion rates.[11] Consequently, pharmaceutical companies

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4. *Patents: Pharmaceutical Product Patenting Strategies*, LEMAN CONSULTING S.A. 1–2, http://www.lemanconsulting.ch/doc/GB_PATENT_Product_patenting_strategies.pdf (last visited Feb. 29, 2016).

5. *Id.*

6. *Id.* at 1.

7. *Id.* at 2.

8. *See* Roger L. Williams, *Dosage Regimen Design: Pharmacodynamic Considerations*, 32 J. CLINICAL PHARMACOLOGY 597, 597–99 (1992) (explaining how "drug effect can be measured in terms of several different positive and negative actions over time"); *Dosage Regimen*, U. LAUSANNE, http://sepia.unil.ch/pharmacology/index.php?id=76 (last visited Feb. 29, 2016).

9. Williams, *supra* note 8, at 598.

10. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: DOSAGE AND ADMINISTRATION SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT 3 (Mar. 2010), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075066.pdf [hereinafter GUIDANCE FOR INDUSTRY: DOSAGE AND ADMINISTRATION].

11. *See, e.g.*, Stephen E. Kimmel, *Warfarin Therapy: In Need of Improvement After All These Years*, 9 EXPERT OP. PHARMACOTHERAPY 677, 680 (2008) ("[A] large proportion of interpatient variability in warfarin response remains unexplained. This variability is consistent with multigenetic effects on drug response."). Another example is Daptomycin (Cubicin), an

invest significantly in research and development to comply with FDA requirements and simplify dosage regimens for increased patient adherence.[12] Failure or delay to file for patent protection on dosage regimens may allow competitors to claim their own invention and affect the brand company's "freedom-to-operate on . . . [the] product under development."[13] Therefore, competent patent attorneys should use dosage regimen patents to ensure optimum protection of pharmaceutical products.

Drug discovery has taken a drastically different trajectory after the introduction of personalized medicine, shifting from exclusively focusing on developing new blockbuster chemical entities to embracing tailored therapeutics.[14] Scientists and medical professionals have long recognized that patients respond to drugs differently, largely influenced by age, gender, genetic makeup, environmental factors, life style, body mass index, and so on.[15] However, the lack of scientific ability to

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antibiotic used to treat infections, including those resistant to vancomycin, a commonly used antibiotic. Its application has not been easy due to various adverse effects upon different patient population. *See* Barry Fox & Sarah E. Bland, *UMHC Guidelines for the Use of Deptomycin (Cubicin®)*, U. WIS. HOSP. & CLINICS (Feb. 2011), http://www.uwhealth.org/files/uwhealth/docs/antimicrobial/Daptomycin.pdf. For a review article explaining common challenges, see Stella M. Davies, *Pharmacogenetics, Pharmacogenomics and Personalized Medicine: Are We There Yet?*, 1 HEMATOLOGY 111, 111 (2006).

12. *Improving Prescription Medicine Adherence is Key to Better Health Care*, PHRMA 6 (Jan. 2011), http://phrma.org/sites/default/files/pdf/PhRMA_Improving%20Medication%20Adherence_Issue%20Brief.pdf. *See generally* Matthew Herper, *How Much Does Pharmaceutical Innovation Cost? A Look At 100 Companies*, FORBES (Aug. 11, 2013, 11:10 AM), http://www.forbes.com/sites/matthewherper/2013/08/11/the-cost-of-inventing-a-new-drug-98-companies-ranked/#91a392616284 (presenting the empirical results of the author's research into the costs of inventing, developing, and ultimately marketing new pharmaceutical drugs).

13. *Patents: Pharmaceutical Product Patenting Strategies supra* note 4, at 3.

14. Rebecca Henderson & Cate Reavis, *Eli Lilly: Recreating Drug Discovery for the 21st Century*, MASS. INST. TECH. SLOAN SCH. MGMT. 1 (Mar. 13, 2008), https://mitsloan.mit.edu/LearningEdge/CaseDocs/07-043-Recreating-Drug-Discovery.pdf.

15. *Personalized Medicine*, NAT'L INST. HEALTH (Oct. 7, 2015), https://www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/personalized-medicine; *see also* U.S. FOOD & DRUG ADMIN., PAVING THE WAY FOR PERSONALIZED MEDICINE: FDA'S ROLE IN A NEW ERA OF MEDICAL PRODUCT DEVELOPMENT 19 (Oct. 2013), http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf [hereinafter PAVING

predict an individual patient's treatment success for most diseases and conditions has forced clinicians "to follow a less than optimal approach to prescribing drugs": one size fits all.[16] Fortunately, rapid technological developments on genomic DNA sequencing have enabled advances in our understanding of human genetics and its influences on disease and treatment.[17] Initiated by the National Human Genome Research Institute, the development of next-generation DNA sequencing technologies brought the cost of the whole human genome sequencing down to $1000 in 2015.[18] This breakthrough will help close the "tremendous gap in human genetic variation data" and treatment response—a giant step towards realizing personalized medicine.[19]

Correlation of drug dosage regimens to specific patients with a particular genetic makeup will allow for optimal treatment results and the development of new uses for known drugs.[20] Therefore, genetic testing must be performed and interpreted by medical professionals before dosage regimens can be determined for individual patients. The testing and interpretation processes will most likely be performed outside of the R&D department of pharmaceutical companies.[21] These developments in personalized medicine will not only raise regulatory challenges, but also restructure the pharmaceutical

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THE WAY FOR PERSONALIZED MEDICINE]. *See generally* W. Ken Redekop & Deirdre Mladsi, *The Faces of Personalized Medicine: A Framework for Understanding its Meaning and Scope*, 16 VALUE IN HEALTH S4, S4 (2013).

16. *See* PAVING THE WAY FOR PERSONALIZED MEDICINE, *supra* note 15, at 6; LJ Lesko, *Personalized Medicine: Elusive Dream or Imminent Reality?*, 81 Clinical Pharmacology & Therapeutics 807, 808 (2007) ("[t]he 'one size fits all' dosing paradigm is not precise enough and new approaches are needed to define the right dose.").

17. PERSONALIZED MED. COALITION, THE CASE FOR PERSONALIZED MEDICINE 4 (4th ed. 2014), http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/pmc_the_case_for_personalized_medicine.pdf.

18. Press Release, George Church, Co-Founder, Veritas Genetics, Veritas Genetics Breaks $1,000 Whole Genome Barrier (Sept. 29, 2015), https://www.veritasgenetics.com/documents/VG-PGP-Announcement-Final.pdf.

19. THE CASE FOR PERSONALIZED MEDICINE, *supra* note 17, at 19–20.

20. *Id*.

21. For a discussion on future landscape of clinical testing in both hospital and independent lab settings, see *The Future for Hospital and Independent Labs in the U.S. Clinical Testing Market*, KALORAMA INFO., http://www.kaloramainformation.com/article/2014-01/Future-Hospital-and-Independent-Labs-US-Clinical-Testing-Market (last visited Mar. 1, 2016).

industry, especially their strategies to patent portfolio management. Section I of this note introduces the background information regarding personalized medicine, dosage regimens, and the emergency of next-generation DNA sequencing technology and its impact on the medical practice. Section II discusses current patent strategies surrounding dosage regimens and the ramifications of individualized prescriptions. Section II also explores the regulatory difficulties FDA confronts with the new sequencing technology and potential policy changes. Section III examines available IP strategies that pharmaceutical companies could adopt to accommodate these changes in a new healthcare era.

I. BACKGROUND

A. DRUG DOSAGE REGIMENS IN PERSONALIZED MEDICINE

A dosage regimen is the modality of drug administration, including formulation, route of administration, drug dose, dosing interval, and treatment duration.[22] Determining the right dosage regimen, paramount to safe and effective drug development, is required by FDA for a new drug application[23] and requires a significant capital investment.[24] Yet, dosage regimens are difficult to define for certain drugs.[25] The most-cited case study involves the drug warfarin, which has been used for the treatment and "long-term prevention of thromboembolism."[26] "It has been more than a half century since the FDA approved warfarin as an oral anticoagulant," but, despite decades of clinical use, rates of "adverse events

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22. *Dosage Regimen*, *supra* note 8; *see also* Williams, *supra* note 8, at 598.

23. *See generally* GUIDANCE FOR INDUSTRY: DOSAGE AND ADMINISTRATION, *supra* note 10, at 2–8 (providing the FDA's detailed guidelines for setting and communicating the dosage regimen of a drug).

24. *See* Millman, *supra* note 1 (discussing the recent study *Cost to Develop and Win Marketing Approval for a New Drug is $2.6 Billion*, TUFTS CTR. FOR STUDY DRUG DEV. (Nov. 18, 2014), http://csdd.tufts.edu/news/complete_story/pr_tufts_csdd_2014_cost_study).

25. *See generally* Dominik Selzer et al., *Finite and Infinite Dosing: Difficulties in Measurements, Evaluations and Predictions*, 65 ADV. DRUG DELIVERY REVS. 278, 278 (2013) (analyzing the problems commonly associated with dosages of drugs that are applied to the skin); *see also* Brian L. Erstad, *Which Weight for Weight-Based Dosage Regimens in Obese Patients?*, 59 AM. J. HEALTH-SYS. PHARMACY 2105, 2105 (2002) (describing the role of a patient's weight in determining proper dosage.

26. Kimmel, *supra* note 11, at 678.

from this well-known drug [are] still among the highest of all commonly prescribed outpatient drugs in the world."[27] Unfortunately, as one of very few available oral drugs for thromboembolism prevention, "warfarin is [also] the tenth most commonly prescribed medication in the US."[28] "Bleeding . . . occurs in up to 41% of patients treated with warfarin," leading to medical complications and deprivation of therapy.[29] The principal issue associated with "administer[ing] warfarin is the biological heterogeneity and comorbidity of the[] patients" and the drug's narrow therapeutic index, which causes "significant interindividual variability" in patients' responses.[30] "Although the [recommended] average maintenance dose is 4 – 6 mg per day, [practically,] there is a very wide range of doses (such as 4.5 – 77 mg per week[]) required to achieve the same [level of anticoagulation control] among different patients."[31] As a result, patients prescribed with warfarin are strongly advised to wear medical alerts.[32] To promote drug safety and protect public health, a better understanding of the multifactorial and multigenetic drug responses from individual patients is of high importance in modern pharmaceutical science.

Traditional drug development and clinical approaches to design dosage regimens vary significantly among different therapeutic areas and a drug's benefit/risk analysis.[33] However, the basic concept is to provide a "simple and easy [dosing paradigm] for physicians and patients to understand and use[, . . . which is frequently] referred to as the "one size fits all" concept of dosing."[34] During the course of treatment, the doctor makes a decision based on the recommended dosing paradigm;

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27. Lesko, *supra* note 16, at 808.

28. Kimmel, *supra* note 11, at 678.

29. *Id*.

30. Lesko, *supra* note 16, at 808; *see also* Elizabeth A. Sconce et al., *The Impact of CYP2C9 and VKORC1 Genetic Polymorphism and Patient Characteristics Upon Warfarin Dose Requirements: Proposal for a New Dosing Regimen*, 106 BLOOD 2329, 2329 (2005) ("Patients are at greatest risk of overanticoagulation during the initiation period . . . . These early problems are due principally to the widespread interindividual variation in response to the warfarin loading dose, explained in part by patient age and genotype.").

31. Kimmel, *supra* note 11, at 679 (footnote omitted).

32. Michael A. Chen, *Taking Warfarin (Coumadin)*, MEDLINEPLUS (Jan. 9, 2015), https://www.nlm.nih.gov/medlineplus/ency/patientinstructions/000292.htm.

33. Lesko, *supra* note 16, at 808.

34. *Id*.

if the medication does not have the desired effect after a few weeks, the patient will be put on a different regimen or a new drug.[35] This "'trial-and error' approach can lead to patient dissatisfaction, adverse drug responses and drug interactions[, delay of treatment,] and poor [patient] adherence to treatment regimens."[36] Warfarin, discussed above, is a paramount example of this concern.[37] The need for a "'therapy with the right drug at the right dose in the right patient'" is highlighted by the fact that "adverse drug reactions may rank as the fifth leading cause of death in the United States."[38] "[A]pproximately 3.1 billion prescriptions are issued in the United States [per year], of which approximately 2.1 million result in an adverse reaction. One million prescriptions form this latter group may result in hospitalization, and of these more than 100,000 patients may die."[39]

Recognizing individual differences in drug responses is an essential step towards optimizing therapy. "A substantial portion of variability in drug response is genetically determined, [requiring consideration of] age, [nutrition, health status, ethnicity, gender,] environmental exposure, and concurrent therapy."[40] Several terms have been used interchangeably with "personalized medicine," one of which, "'precision medicine,' is perhaps most synonymous and has been defined by the National Academy of Science (NAS) as 'the use of genomic, epigenetic, exposure and other data to define individual patterns of disease, potentially leading to better individual treatment.'"[41] Such precision medicine is achieved by a stratification process that divides "patients with a particular disease into subgroups, based on a characteristic of some sort,

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35. *See* PAVING THE WAY FOR PERSONALIZED MEDICINE, *supra* note 15, at 6.

36. *Id*.

37. *Supra* text accompanying notes 27–32.

38. Laviero Mancinelli, Maureen Cronin & Wolfgang Sadée, *Pharmacogenomics: The Promise of Personalized Medicine*, 2 AAPS PHARMSCI 1, 2 (2000).

39. *Id*. at 10.

40. *Id*. at 1.

41. *See* PAVING THE WAY FOR PERSONALIZED MEDICINE, *supra* note 15, at 6. For a thorough discussion of the scope and definition of personalized medicine, see W. Ken Redekop & Deirdre Mladsi, *The Faces of Personalized Medicine: A Framework for Understanding Its Meaning and Scope*, 16 VALUE IN HEALTH S4 (2013).

who respond more frequently to a particular drug or, alternatively, are at a decreased risk of side effects."[42] Then, dosage regiments are designed specifically for a subgroup instead of for all patients.[43]

Personalized medicine has been proposed to revolutionize modern healthcare and medical practice in several ways.[44] First, it "introduces the ability to use molecular markers that signal disease risk" and shifts the focus from treatment to "prevention and early intervention."[45] A good example is found in "women with certain *BRCA1* or *BRCA2* gene variations" who, compared to the general female population, have a much higher chance of developing breast (85% v. 13%) and ovarian cancers (60% v. 1.7%).[46] Through genetic testing, patients can benefit from suggested preventive measures including "lifestyle changes and disease-monitoring options."[47] Secondly, personalized medicine will guide dosage regimen design and "reduce trial-and-error prescribing," thus decreasing adverse effects.[48] Studies have shown that "38 percent of depression patients, 50 percent of arthritis patients, 40 percent of asthma patients, and 43 percent of diabetic patients will not respond to initial treatment" positively.[49] "The majority of patients, for example, have at least one DNA-based variation in the enzymes that metabolize half of the most commonly prescribed medicines."[50] Thus, "[t]he use of genetic . . . screening allows

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42. *See* PAVING THE WAY FOR PERSONALIZED MEDICINE, *supra* note 15, at 6, 8 ("Stratification can be thought of as a core element of personalized medicine.").

43. *Id*.

44. *See generally* Alan Haruo Bryce & Robert McWilliams, *Current Status and Future Directions of Personalized Medicine*, 5 GENOME MED. 62 (2013) (providing an overview of major topics evolving in personalized medicine, including genomic techniques and their clinical applications as well as relevant regulatory implications); *see also* Fatiha H. Shabaruddin, Nigel D. Fleeman & Katherine Payne, *Economic Evaluations of Personalized Medicine: Existing Challenges and Current Developments*, 8 PHARMACOGENOMICS & PERSONALIZED MED. 115, 115 (2015) ("It is often argued that personalizing treatment will inevitably improve clinical outcomes for patients and help achieve more effective use of health care resources.").

45. THE CASE FOR PERSONALIZED MEDICINE, *supra* note 17, at 8.

46. *Id*.

47. *Id*. at 8–9.

48. *Id*. at 9.

49. *Id.*

50. *Id.*

the physician to select an optimal therapy the first time," increasing patient adherence and avoiding high costs.[51]

At the core of personalized medicine are more accurate and individualized dosage regimen designs, which take the center stage of technical advances[52] and are guided by pharmacogenomics, "the study of variations of DNA and RNA characteristics [(genomics)] as related to drug response."[53] The first big scientific driver in personalized medicine was the discovery of cytochrome P450 metabolic enzymes and their role in chemically modifying the drug molecules so they can be removed from the bloodstream; thus, variations in these enzymes can have significant impacts on the effective dosage regimens of the drug.[54] The next real drive occurred with the sequencing of the whole human genome in 2003, which cost $2.7 billion and took thirteen years to complete.[55] The cost and time for sequencing human genomes have declined over the years, but we still face challenges to fully implement these

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51. *Id.* For more examples of genetic-based drug response, see LM Mangravite et al., *Clinical Implications of Pharmacogenomics of Statin Treatment*, 6 PHARMACOGENOMICS J. 360, 360, 369 (2006) (evaluating the role of genetics in statin pharmacogenomics); Mark J. Rieder et al., *Effect of VKORC1 Haplotypes on Transcriptional Regulation and Warfarin Dose*, 352 NEW ENG. J. MED. 2285, 2285 (2005) ("Variants in the gene encoding vitamin K epoxide reductase complex 1 (*VKORC1*) may affect the response to warfarin."); Steven G. Terra et al., *β_1-Adrenergic Receptor Polymorphisms and Left Ventricular Remodeling Changes in Response to β-Blocker Therapy*, 15 PHARMACOGENETICS & GENOMICS 227, 233 (2005) ("If confirmed in future studies, particularly those evaluating clinical outcomes, targeted heart failure therapy based on an individual genotype might be done at some point in the future. Given the number of standard therapies now available for heart failure, such an approach might allow for more rational prescribing, and use of alternative therapies in those patients deriving minimal benefit from a ß-blocker.").

52. PAVING THE WAY FOR PERSONALIZED MEDICINE, *supra* note 15, at 6. *See generally* Marilyn N. Martinez et al., *Dosing Regimen Matters: The Importance of Early Intervention and Rapid Attainment of the Pharmacokinetic/Pharmacodynamic Target*, 56 ANTIMICROBIAL AGENTS & CHEMOTHERAPY 2795, 2795, 2804 (2012).

53. PAVING THE WAY FOR PERSONALIZED MEDICINE, *supra* note 15, at 8.

54. Ulrich M. Zanger & Matthias Schwab, *Cytochrome P450 Enzymes in Drug Metabolism: Regulation of Gene Expression, Enzyme Activities, and Impact of Genetic Variation*, 138 PHARMACOLOGY & THERAPEUTICS 103, 104 (2013).

55. *The Human Genome Project Completion: Frequently Asked Questions*, NAT'L HUM. GENOME RES. INST., http://www.genome.gov/11006943 (last updated Oct. 30, 2010).

technologies in a clinical setting and effectively correlate the data with dosage regimen design.[56]

B. NEXT-GENERATION DNA SEQUENCING TECHNOLOGY

Recent efforts in clinical implementation of pharmacogenomics have proved to be challenging, some of the chief reasons including: delay in genomic testing, "lack of . . . large-scale genomic data linked to automated clinical decision support, . . . uncertainty of clinical benefits . . . for genome-guided therapy, and . . . financial concerns with regard to genomic medicine."[57] These difficulties can, to a certain extent, be attributed to deficiencies in current human genome sequencing technologies.[58] For example, the long delay and high cost to perform a sequencing test deter these efforts, resulting in too little data collected to make meaningful correlations between genetic variations and optimal clinical decisions.[59] Therefore, a groundbreaking improvement in human genome sequencing technology is a vital part of successful implementation of personalized medicine.

DNA sequencing technology has a rich and diverse history, and it embodies interplay among chemistry, engineering, software, and molecular biology.[60] "The first two widely-known

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56. *See* Nan Myers, *The Challenges of Personalized Medicine*, PENN MED. Spring 2009, at 14–15, http://www.uphs.upenn.edu/news/publications/PENNMedicine/files/PENNMedicine_2009_02_spring14_personalized_medicine.pdf ("'People have an incredible optimism for personalized medicine' [b]ut . . . the reality today is very different. It is a very complicated process, both creating a test and getting the test to the point where it can actually be used in a clinical setting.") (quoting Dr. Pamela Sankar, assistant professor of bioethics at Penn's Center for Bioethics); *see also* Casey Lynnette Overby & Peter Tarczy-Hornoch, *Personalized Medicine: Challenges and Opportunities for Translational Bioinformatics*, 10 PERSONALIZED MED. 453, 458–59 (2013) (summarizing the challenges and conclusions about the future of personalized medicine).

57. *See* Suzette J. Bielinski et al., *Preemptive Genotyping for Personalized Medicine: Design of the Right Drug, Right Dose, Right Time—Using Genomic Data to Individualize Treatment Protocol*, 89 MAYO CLINIC PROC. 25, 26 (2014).

58. *Id.*; *see* Shabaruddin, Fleeman & Payne, *supra* note 44, at 116.

59. Myers, *supra* note 56, at 15; Shabaruddin, Fleeman & Payne, *supra* note 44, at 123.

60. *See* Lisa D. White, *History of DNA Sequencing Technologies*, *in* Next Generation Sequencing: Translation to Clinical Diagnostics 10 (Lee-Jun C. Wong ed., 2013); Clyde A. Hutchison III, *DNA Sequencing: Bench to Bedside*

methods for DNA sequencing appeared in 1977": the Maxam-Gilbert and Sanger sequencing methods, both relying on separation of DNA fragments with gel electrophoresis.[61] Both methods suffer from a demand for large quantities of materials, low accuracy, and high labor intensity.[62] Due to its superior simplicity and reliability, Sanger sequencing became the dominant method in the 1990s, especially after the incorporation of fluorescence labeling and capillary instrument.[63] Coupled with advances of computer science, these "second-generation DNA sequencing instruments were taken up broadly by the research market" by 2008 after the cost of "whole-genome sequencing costs fell from between $100–$300 million in 2001 to about $10 million in 2007."[64]

As a response to an initiative from the National Human Genome Research Institute that aimed at developing sequencing technology of the entire genome for less than $1000, the industry devoted significant efforts to developing sequencing technologies at a much faster rate than ever experienced.[65] The resulting next-generation sequencing technologies feature characteristics such as low cost, fast analysis, high accuracy, and low sample volume.[66]

For example, in May 2011, Illumina announced that it had lowered the price for sequencing the whole human genome to $5000 per individual[67] and in January 2014 introduced a new

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and Beyond, 35 NUCLEIC ACIDS RES. 6227, 6227–31 (2007); Miodrag Gužvić, *The History of DNA Sequencing*, 32 J. MED. BIOCHEMISTRY 301, 302 (2013).

61. Gužvić, *supra* note 60, at 302.

62. *Id*. at 302–04.

63. *Id*. at 304; Elaine R. Mardis, *Next-Generation Sequencing Platforms*, 6 ANN. REV. ANALYTICAL CHEMISTRY 287, 290 (2013).

64. THE CASE FOR PERSONALIZED MEDICINE, *supra* note 17, at 18.

65. Press Release, Nat'l Hum. Genome Res. Inst., NHGRI Seeks Next Generation of Sequencing Technologies: New Grants Support Development of Faster, Cheaper DNA Sequencing (Oct. 14, 2004), https://www.genome.gov/12513210; Jason M. Rizzo & Michael J. Buck, *Key Principles and Clinical Application of "Next-Generation" DNA Sequencing*, 5 CANCER PREVENTION RES. 887, 887 (2012); *see also* Chandran Anandhakumar et al., *Advancing Small-Molecule-Based Chemical Biology with Next-Generation Sequencing Technologies*, 16 CHEMBIOCHEM 20, 36 (2015); Mardis, *supra* note 63, at 288, 300–01.

66. Mardis, *supra* note 63, at 288, 300.

67. Bio-IT World Staff, *Illumina Announces $5,000 Genome Pricing*, BIOIT WORLD (May 9, 2011), http://www.bio-itworld.com/news/05/09/2011/Illumina-announces-five-thousand-dollar-genome.html. "IGN [Illumina Genome Network] is a global service partnership that links researchers

instrument that can do the same job for just $1000.[68] The Illumina platform combines DNA biology and fluorescence detection to achieve high throughput and accuracy.[69] In spring 2014, Oxford Nanopore announced their MinION Access Program to call research communities and industries to test their $1000 whole genome sequencer.[70] Nanopore technology uses electrical fields to drive negatively charged DNA through a nanometer channel, and the resulting electrical signatures reveal the sequence of the DNA.[71] With bioinformatics and long MinION reads, scientists were able to achieve 99% accuracy and resolve a cancer-testis gene family.[72] In September 2015, Veritas Genetics, as a part of the Personal Genome Project, announced a $1000 full-genome sequencing service including data interpretation.[73] The Personal Genome Project is dedicated to creating open public genome and health data for the greater good.[74] Thermo Fisher Scientific also entered the

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interested in conducting large-scale whole human genome projects with leading institutions that can perform such projects using Illumina sequencers." *Id.*

68. Matthew Herper, *The $1,000 Genome Arrives—For Real, This Time*, FORBES (Jan. 14, 2014, 9:14 PM), http://www.forbes.com/sites/matthewherper/2014/01/14/the-1000-genome-arrives-for-real-this-time/#388d378b61c9.

69. Anandhakumar et al., *supra* note 65, at 22; Press Release, Illumina, Inc., Illumina Expands World's Most Comprehensive Next-Generation Sequencing Portfolio (Jan. 12, 2015), http://www.illumina.com/company/news-center/press-releases/press-release-details.html?newsid=2006979; *see also* Roadmap Epigenomics Consortium et al., *Integrative Analysis of 111 Reference Human Epigenomes*, 518 NATURE 317, 317 (2015).

70. Julia Karow, *Oxford Nanopore to Select First Users for Early Access to MinIon; Program 'Heavily Oversubscribed*,*'* GENOMEWEB (Jan. 28, 2014), https://www.genomeweb.com/sequencing/oxford-nanopore-select-first-users-early-access-minion-program-heavily-oversubsc.

71. Ron Ammar et al., *Long Read Nanopore Sequencing for Detection of* HLA *and* CYP2D6 *Variants and Haplotypes*, 4 F1000RES. 17, 17 (2015); Miten Jain et al., *Improved Data Analysis for the MinION Nanopore Sequencer*, 12 NATURE METHODS 351, 351 (2015).

72. Jain et al., *supra* note 71, at 351.

73. Alexandra Ossola, *Your Full Genome Can Be Sequenced and Analyzed for Just $1,000*, POPULAR SCI. (Sept. 30, 2015), http://www.popsci.com/cost-full-genome-sequencing-drops-to-1000.

74. *Sharing Personal Genomes*, PERS. GENOME PROJECT: HARV., http://www.personalgenomes.org (last visited Jan. 30, 2016).

competitive industry by providing three types of whole genome sequencers that cost around $1000.[75]

Meanwhile, other biotechnology companies are also getting close to fast and inexpensive whole genome sequencing in this heated race. Pacific Biosciences announced their Sequel Sequencing System in September 2015 with an important feature of detecting epigenetic markers in the genome in addition to the natural sequence.[76] Understanding the epigenetic disorder provides another dimension into correlating genetic variations to disease states, although the current $350,000 cost of the system is much higher than sister technologies.[77] It is worth noting, however, that additional costs and time are necessary for all analysis and annotation in a clinical setting.

The next-generation DNA sequencing market is growing rapidly and is "expect[ed] to grow from its current size of 2.2 billon to 5.6 billion" this year.[78] Current market leader Illumina enjoyed revenue growth of approximately 30% in 2014.[79] Roche shook hands with Foundation Medicine in an agreement worth nearly $1.2 billion.[80] Pharmaceutical companies have also recognized the potential benefits of next-generation sequencing; "[d]uring just part of 2015, Genentech announced two agreements, and Pfizer announced one."[81] The large investments and intensive research efforts pouring into the field prompt the following question: will the fast advance of

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75. *Whole Genome Sequencing*, THERMOFISHER SCI., https://www.thermofisher.com/us/en/home/life-science/sequencing/dna-sequencing/whole-genome-sequencing.html (last visited Jan 30, 2016).

76. *PacBio Announces Sequel Sequencing System*, BIOIT WORLD (Sept. 30, 2015), http://www.bio-itworld.com/2015/9/30/pacbio-announces-sequel-sequencing-system.aspx.

77. *Id.*; *see also* Mark J. P. Chaisson et al., *Resolving the Complexity of the Human Genome Using Single-Molecule Sequencing*, 517 NATURE 608, 608 (2015).

78. *Next Generation Sequencing (NGS) Markets 2015*, PR NEWSWIRE (Mar. 5, 2015), http://www.prnewswire.com/news-releases/next-generation-sequencing-ngs-markets-2015-300046436.html.

79. *Id.*; *see also* Press Release, Markets & Markets, Next Generation Sequencing (NGS) Market Worth 10,371.1 Million USD by 2021, (Mar. 9, 2016), http://www.marketsandmarkets.com/PressReleases/ngs-technologies.asp.

80. *See Next Generation Sequencing (NGS) Markets 2015*, *supra* note 78.

81. *Id.*

next-generation DNA sequencing bring personalized medicine to patients soon?

C. DOSAGE REGIMEN DESIGN IN THE ERA OF NEXT-GENERATION DNA SEQUENCING

"Thanks to the significant decrease in sequencing costs and time afforded by NGS [next-generation sequencing] technologies, it is becoming more cost-effective to resequence entire human genomes from clinical samples and this will soon be routine in the clinical practice of medicine."[82] Currently, targeted genetic tests are predominantly used as diagnostic and prognostic tools in clinical oncology due to their low cost and relatively simple interpretability.[83] But, importantly, whole genome sequencing requires no prior selection of particular genes to be profiled and provides a global view of the genome, which allow for the identification of novel alternations and somatic mutations even in non-coding and unannotated regions of the genome.[84] "High-coverage genomic data also allows for the detection of chromosomal rearrangements . . . . [and because t]he identity and distribution of genomic alterations vary widely between cancer types, . . . mutational signatures[] can be indicative of the underlying risk of cancer development."[85] For example, the authors in a 2011 case study, in the course of treating a very difficult disease, identified an abnormal gene rearrangement using next-generation

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82. Rizzo & Buck, *supra* note 65, at 895; Eric D. Green, Mark S. Guyer & Nat'l Hum. Genome Res. Inst., *Charting a Course for Genomic Medicine from Base Pairs to Bedside*, 470 NATURE 204, 205 (2011); Stephen F. Kingsmore & Carol J. Saunders, *Deep Sequencing of Patient Genomes for Disease Diagnosis: When Will it Become Routine?*, 3 SCI. TRANSLATIONAL MED. 23, 1 (2011); *see* RICHARD TUTTON, GENOMICS AND THE REIMAGINING OF PERSONALIZED MEDICINE 153 (Ashgate ed., 2014); Joseph V. Thakuria, *Principles and Clinical Applications of Next-Generation DNA Sequencing*, UPTODATE (July 27, 2015), http://www.uptodate.com/contents/principles-and-clinical-applications-of-next-generation-dna-sequencing; *see also* Leslie G. Biesecker & Robert C. Green, *Diagnostic Clinical Genome and Exome Sequencing*, 370 NEW ENG. J. MED. 2418, 2423 (2014); Christian Gilissen et al., *Genome Sequencing Identifies Major Causes of Severe Intellectual Disability*, 511 NATURE 344, 344 (2014).

83. Rizzo & Buck, *supra* note 65, at 895.

84. *Id.*

85. Veronique G. LeBlanc & Marco A. Marra, *Next-Generation Sequencing Approaches in Cancer: Where Have They Brought Us and Where Will They Take Us?*, 7 CANCERS 1925, 1930 (2015).

technology to sequence the whole genome early on and successfully altered the treatment plan in a clinically relevant time frame.[86] Importantly, the genetic rearrangement was not detectable using standard targeted sequencing.[87]

In addition to genome analysis, next-generation sequencing can also be used to monitor gene expression, which is particularly important for detecting "cancer, a disease characterized by global genomic dysregulation."[88] Pacific Bioscience, along with other companies, has developed a system that can detect epigenetic modifications, the identity and pattern of which regulate a variety of cellular functions and progress of cancer.[89] For example, an ovarian cancer study used next-generation sequencing technology to monitor the epigenetic difference between healthy and diseased individuals and found a modification trend in patients at an area close to a particular gene.[90] Next-generation sequencing technology has provided scientists and medical professionals unprecedented access to the whole human genome at a cost of approximately $1000.

As proponents of personalized medicine envision a future where every person will have his or her whole genome sequenced and linked to his or her medical record, allowing physicians to develop a more holistic, personalized health care strategy, there still remain obstacles to overcome. First, "our ability to collect data outpaces the medical community's ability to understand and act on it."[91] Second, more available sequencing data allows better understanding of disease and cancers caused by genetic variations, but it does not directly answer the question of how patients with a particular genetic makeup will respond to a drug.[92] More data and research are

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86. John S. Welch et al., *Use of Whole-Genome Sequencing to Diagnose a Cryptic Fusion Oncogene,* 305 JAMA 1577, 1578–79 (2011).

87. *Id.* at 1579.

88. LeBlanc & Marra, *supra* note 85, at 1931.

89. *See PacBio Announces Sequel Sequencing System*, *supra* note 76; *see generally* Samantha Bhat et al., *Biological Implications and Therapeutic Significance of DNA Methylation Regulated Genes in Cervical Cancer*, 121 BIOCHIMIE 298, 300 (2016); Javier Soto et al., *The Impact of Next-Generation Sequencing on DNA Methylation-Based Translational Cancer Research*, 169 TRANSLATIONAL RES. 1, 8 (2016).

90. Soto et al., *supra* note 89, at 13.

91. THE CASE FOR PERSONALIZED MEDICINE, *supra* note 17, at 20.

92. Myers, *supra* note 56, at 15.

necessary to fully appreciate these correlations, but open and public sharing of an individual's genomic data raises significant privacy issues.[93] Over time, health information technology will advance, while researchers identify genetic variations that correlate to disease and treatment response. And through coalitions like the Personal Genome Project and legislative efforts, personalized medicine will become a reality.

II. ANALYSIS

A. IMPACT OF PERSONALIZED MEDICINE ON DOSAGE REGIMEN PATENTS

The cost of developing a new drug depends on the type of drug, the success rate, and whether the drug is a new molecular entity (NME) or "an incremental modification of an existing drug."[94] The research "cost of developing an innovative new drug . . . [is] more than $800 million," while most incrementally modified drugs cost less.[95] Adding marketing, regulatory approval processes, and other expenses, recent studies have shown that a successful launch of a new drug costs, on average, $2.6 billion.[96] Obtaining approval from the DA to market the drug takes years to complete; more often than not, pharmaceutical companies find themselves quickly running out of patent terms on their newly-launched product.[97] Therefore, strategies to preserve and extend market exclusivity become paramount for pharmaceutical companies to acquire sufficient returns to recoup investment and fund further research.[98]

Building a strong patent portfolio is one essential part of that strategy, which includes both basic protection of the chemical entity (if it is a NME drug) and follow-on patents

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93. M. Leeann Habte, Claire M. Marblestone & Jennifer M. Forde, *Privacy Issues in the Sharing of Genetic Information*, FOLEY & LARDNER LLP, Sept. 2014, at 1, https://www.foley.com/files/Publication/7465587b-5df9-4f85-9969-68ce1b4c39af/Presentation/PublicationAttachment/88ba6035-c031-4ff4-b4e2-6ad15030b17d/PrivacyIssuesintheSharingofGeneticInformation.pdf.

94. CONG. BUDGET OFF., RESEARCH AND DEVELOPMENT IN THE PHARMACEUTICAL INDUSTRY 1, 2 (2006), https://www.cbo.gov/sites/default/files/109th-congress-2005-2006/reports/10-02-drugr-d.pdf.

95. *Id*. at 2.

96. Millman, *supra* note 1.

97. Hathaway, Manthei & Scherer *supra* note 2, at 34.

98. Herschbach Jarrell & Asher, *supra* note 3.

regarding improvements and new developments.[99] For incrementally modified drugs, only follow-on patents are available under most circumstances.[100] Among these secondary filings, dosage regimens of the drug are commonly used, not only because the FDA requires research data on the proper administration of the drug, but also due to its large strategic value.[101] Dosage regimens are difficult to determine, as demonstrated in the warfarin example discussed above,[102] thus, a large amount of money has to be spent to understand the drug's toxicity and efficacy in various dosage regimens. Branded drug companies naturally desire patent protection on these discoveries.

More importantly, skilled patent attorneys use dosage regimen patents in various strategies. First, more patents on a product, basic and secondary, increases the possibility of findings of validity, enforceability, and infringement in future litigation which strengthens the portfolio and diminishes uncertainty.[103] Secondly, competitors could file for these patents and raise freedom-to-operate issues for the branded drug owner.[104] Lastly, a lengthy FDA approval process cuts deeply into the term of a patent family; companies often have very few years of exclusivity left at the beginning of product launch.[105] With a remarkable number of "'blockbuster' drugs" losing their patent protection in the next few years, companies are desperate for any possible extension or continuation of their exclusivity.[106] Once a chemical composition is patented, it becomes a "prior art reference" to any additional patent application based around the compound or pharmaceutical composition.[107] Therefore, "the new patent protections generally encompasses narrow improvements or new uses for

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99. *Patents: Pharmaceutical Product Patenting Strategies*, *supra* note 4, at 1.

100. *See id.*

101. *Id.* at 1, 4–5.

102. Kimmel, *supra* note 11, at 3.

103. *See Patents: Pharmaceutical Product Patenting Strategies*, *supra* note 4, at 4–5.

104. *Id.* at 5.

105. Hathaway, Manthei & Scherer *supra* note 2, at 34.

106. Michelle L. Cunningham & W. Murray Spruill, *Strategies for Extending the Life of Patents*, 18 BIOPHARM, no. 3, Mar. 1, 2005, http://www.biopharminternational.com/strategies-extending-life-patents.

107. *Id.*

the pharmaceutical [compound] not disclosed or suggested in the original patent."[108]

For example, new applications can be filed for new routes of administration or dosing form to prevent adverse effect and increase efficacy.[109] The migraine drug Imitrex gained its owner GlaxoSmithKline (GSK) annual sales of $1 billion dollars; after the original patent directed to the compound expired in 2006, GSK sought patent protection and FDA approval on a new Imitrex for intranasal delivery.[110] Alternatively, "several pharmaceutical companies have successfully obtained patent protection for new methods of use."[111] The two most famous examples are finasteride and atomoxetine.[112] Merck first patented and obtained FDA approval on "finasteride as a treatment for benign prostate enlargement under the brand name Proscar. Additional patent protection and FDA approval were sought when a new use for finasteride—treating male pattern baldness—was identified . . . . [and] marketed under the brand name Propecia."[113] Similarly, Eli Lilly "initially investigated [atomoxetine] as a treatment for depression" and later discovered its efficacy in treating attention deficit hyperactivity disorder.[114] Lilly sought additional patent protection and FDA approval for the new use, bringing in more than two million prescriptions within first nine months on the market.[115] These strategies and corresponding examples all relate to alternations of dosage regimens to generate new products and additional patent protection.

With the fast approach of personalized medicine, the use of two medical products is usually involved: "a diagnostic device and a therapeutic product."[116] Genetic testing will first be conducted and interpreted before the doctor translates that information into a sound treatment plan with an optimal

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108. *Id.*
109. *Id.*
110. *Id.*
111. *Id.*
112. *Id.*
113. *Id.*
114. *Id.*
115. *Id.*
116. *See* PAVING THE WAY FOR PERSONALIZED MEDICINE, *supra* note 15, at 8.

dosage regimen.[117] Patients respond to drugs differently and as a result, these dosage regimens cannot be determined until genetic testing is performed.[118] And instead of at the research and development department of a pharmaceutical company, these tests will be done in a hospital or a healthcare facility long after the product has been on the market.[119] Additionally, "the advent of mobile and wireless capability . . . allow for more effective patient monitoring and treatment outside the traditional medical care settings," potentially moving into a patient's home and work.[120] What does this mean for the dosage regimen patents that are so valuable to pharmaceutical companies?

B. CURRENT JURISPRUDENCE ON DRUG DOSAGE REGIMEN PATENTS

Unlike European countries, Japan, and China, dosage regimen patents are treated as medical methods and considered patentable subject matter in the US.[121] However,

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117. *Id*. at 6.

118. *Id.*

119. *Id.* at 9.

120. *Id*.

121. Jerry I-H Hsiao & Wei-Lin Wang, *Dosage Patenting in Personalized Medicine*, B.C. INTELL. PROP. & TECH. F. 7–10 (2012), http://bciptf.org/wp-content/uploads/2012/06/Dosage_Patenting_in_Personalized_Medicine.pdf. Note, however, that Japan's laws are showing slight movement toward the United States approach. *Id.* at 9. For patent law regarding dosage regimens in other countries, *see* European Patent Convention, Convention on the Grant of European Patents art. 54, Oct. 5, 1973, https://www.epo.org/law-practice/legal-texts/html/epc/2013/e/ar54.html; R. Stephen Crespi, *Inventiveness in Biological Chemistry: An International Perspective*, 73 J. PAT. & TRADEMARK OFF. SOC'Y 351, 365–68 (1991) (discussing the European Patent Office guidelines for patentability); Martin Maclean, *Dosage Regimen Patent Claims in Europe*, INTELL. PROP. TODAY, Sept. 2009, at 17; Oksana Mitnovetski & Dianne Nicol, *Are Patents for Methods of Medical Treatment Contrary to the Ordre Public and Morality or "Generally Inconvenient?"*, 30 J. MED. ETHICS 470, 471–74 (2004); *see also* Bristol-Myers Squibb Co. v. Baker Norton Pharmaceuticals Inc. and Napro Biotherapeutics Inc., [2001] EWCA (Civ) 414, http://www.bailii.org/ew/cases/EWCA/Civ/2001/414.html; Actavis UK Ltd. v. Merck & Co. Inc., [2008] EWCA (Civ) 444, http://www.eplawpatentblog.com /2010/February/%5B2008%5D%20EWCA%20Civ%20444.pdf; Nobuta Yokota, LIFE SCI. IP FOCUS, JAPAN: PATENT ELIGIBILITY EXPANDED 25–27 (7th ed., , 2009), http://www.kyowapatent.co.jp/en/info/data/091026.pdf; *Invitation for Public Comments on Draft Revision of Examination Guidelines for "Industrially Applicable Inventions" and Draft Revision of Examination Guidelines for "Medicinal Inventions,"* JAPAN PAT. OFF. (Aug 6, 2009),

the rapid change in patent law has posted great challenges to dosage regimen patents. The first seminal case was *KSR*, which reshaped the non-obviousness jurisprudence of patent law.[122] Before *KSR*, the *Graham* factors were used to test the obviousness of the invention by showing that a skilled artisan in the art would have been motivated to combine the teachings of the prior art references to achieve the claimed invention with a reasonable expectation of success, which was called the "teaching-suggestion-motivation" test.[123] The U.S. Supreme Court rejected the rigid *Graham* test in *KSR* and instead looked for a broad range of indicators: an apparent reason to combine known elements, including market pressure with finite number of solutions, useful technology for improving similar devices, obvious to try, the old teaching-suggestion-motivation test, and so on.[124] This new standard has been a much harder test to fulfill for dosage regimen applications, because they can be easily characterized as arising out of known techniques, obvious to try, or based on teaching-suggestion-motivations from prior art.[125]

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https://www.jpo.go.jp/cgi/linke.cgi?url=/iken_e/comments_iryou.htm; Amy Feng, *Take Local Practice Into Account*, MANAGING INTELL. PROP. (June 1, 2008), http://www.managingip.com/Article/1941461/Take-local-practice-into-account.html; John A. Tessensohn & Shusaku Yamamoto, *Japanese Biotech Patenting Strategies in the Era of Follow-on Biologics*, 28 BIOTECHNOLOGY L. REP. 483, 484–85 (2009) (discussing Japanese follow-on biologics guidelines); Peter K. Yu, *From Pirates to Partners: Protecting Intellectual Property in China in the Twenty-First Century*, 50 AM. U. L. REV. 131, 132–54 (2000) (discussing the change in China's policies toward intellectual property in response to US trade sanctions following World War II).

122. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 420 (2007) (holding that the obviousness inquiry should consider whether the invention was obvious from the view point of one having ordinary skill in the art).

123. *Id.* at 406–07 (citing Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17–18 (1966)).

124. *Id.* at 414–22.

125. Enzo Furrow, *Analyzing the Laws, Regulations, and Policies Affecting FDA-Regulated Products: Pharmaceutical Patent Life-Cycle Management After* KSR v. Teleflex, 63 FOOD & DRUG L. J. 275, 301–06 (2008) (discussing the non-obviousness requirement as it applies to pharmaceuticals). For a new dosage regimen patent that was held non-obvious, see generally Braintree Lab., Inc. v. Novel Lab., Inc., 749 F.3d 1349, 1359 (Fed. Cir. 2014). For new dosage regimen patents that were held obvious, see Allergan, Inc. v. Sandoz, Inc., 726 F.3d 1286, 1288 (Fed. Cir. 2013); Bayer Healthcare Pharmaceuticals, Inc. v. Watson Pharmaceuticals, Inc., 713 F.3d 1369, 1377 (Fed. Cir. 2013); Hoffmann-La Roche, Inc. v. Apotex, Inc., 748 F.3d 1326, 1335 (Fed. Cir. 2013); Warner Chilcott Co. v. Teva Pharmaceuticals USA, Inc., 37 F.Supp.3d 731, 740 (D. Del. 2014).

One recent decision that demonstrates the vigorousness of the *KSR* test in dosing patents is *Warner Chilcott*.[126] The patent owner brought suit against the generic drug company for infringing two patents, which were directed to a delayed-release formulation of the osteoporosis drug Atelvia.[127] The new formulation combined the active ingredient risedronate with ethylene diamine tetraacetic acid (EDTA) and was developed to address a non-absorption problem that occurred with osteoporosis drugs taken with food.[128] The presence of calcium in common food captures the active ingredient in the drug, preventing it from entering the bloodstream; EDTA in the new formulation is able to chelate with calcium and blocks its reaction with the active ingredient.[129] The closest prior art disclosed two mechanisms for increasing absorption with EDTA: (1) chelation, as described above; and (2) permeability enhancement, a process in which "large doses of EDTA spread the pathways between intestinal cells, allowing more . . . [risedronate to enter] into the bloodstream."[130] The patented invention chose to use the first mechanism instead of the second one.[131]

The court reasoned that the prior art contained all the necessary elements and known ways to arrange them and determined that a skilled artisan would be motivated to avoid using large amount of EDTA (second mechanism); therefore, despite the finding of a long-felt, unmet need in the market and *defendant's* own skepticism of this method, the invention was ruled to have produced expected results and was obvious.[132] This ruling underlines the high non-obviousness standard *KSR* created for dosage regimen patents and highlights the uncertainty the smacks of hindsight can impose on a multimillion-dollar product.

The second set of landmark decisions, *Mayo* and *Myriad Genetics*, addressed patent-eligible subject matter for dosage

126. Warner Chilcott Co. v. Teva Pharmaceuticals USA, Inc., 89 F. Supp. 3d 641 (D. N.J. 2015).
127. *Id.* at 646–47.
128. *Id* at 646.
129. *Id* at 645.
130. *Id* at 646.
131. *Id.*
132. *Id.* at 680–82.

regimen and diagnostic tools under 35 U.S.C. § 101.[133] In *Mayo*, the patent was directed to a method of optimizing a patient's dosage regimen of thiopurine drugs by administering the drug to a patient and determining the level of drug metabolites in the patient's body, which would indicate whether the dosage should be increased or decreased.[134] The Court unanimously held that these metabolic diagnostic claims for detecting a correlation between a metabolite and the likelihood of responding to a drug are unpatentable laws of nature and affirmed that the machine-and-transformation test is not the exclusive test for patentability.[135] *Mayo* also devised a two-part test for those claims that claim patent-eligible applications of laws of nature: first, determine whether the claims at issue are directed to a patent-ineligible concept.[136] If the answer is yes, then we next consider the elements of each claim both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a "patent-eligible application."[137] Since using the correlation between dosage and metabolite levels in the blood to optimize one's dosage regimen was purely conventional and obvious, it was insufficient to transform the invention into a patentable subject matter.[138]

Soon after *Mayo*, *Myriad* addressed claims directed to isolated DNA sequences including *BRCA1* and *BRCA2* genes and corresponding human-made cDNAs in which the variations of these sequences indicated the likelihood of an individual to develop breast or ovarian cancer.[139] The Supreme Court held that isolated genomic DNA sequences are natural products and ineligible for patent protection, while cDNA is patent-eligible subject matter.[140] In a subsequent case, the Federal Circuit

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133. Mayo Collaborative Servs. v. Prometheus Lab., Inc., 132 S. Ct. 1289 (2012); Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107 (2013); *see also* 35 U.S.C. § 101 (2012).

134. *Mayo*, 132 S. Ct. at 1294–95.

135. *Id.* at 1303 (stating the "machine-or-transformation" test does not trump the "law of nature" exclusion).

136. *Id.* at 1297–98.

137. *Id.*

138. *Id.* at 1297; *see also* Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (2015).

139. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2112–13 (2013).

140. *Id.* at 2118–19.

also held the method claims of comparing a patient's *BRCA* with wild-type *BRCA* genes to identify mutations as unpatentable subject matter under the *Mayo* framework.[141]

The *Mayo* and *Myriad* cases reshaped the subject-matter eligibility landscape under 35 U.S.C. § 101 (2012) and narrowed the scope of the initial screening for patent eligibility. They raised many uncertainties about how this expanded law-of-nature concept will affect patent protection of diagnostic methods relying on the correlations between a biomarker or genetic traits and certain physiological conditions, such as responses to drugs. The progenies *PerkinElmer* and *Ariosa* highlight the outcry from biotech and pharmaceutical companies.[142]

First, soon after the *Mayo* decision, the Federal Circuit invalidated a diagnostic claim under the two-part test.[143] This claim in *PerkinElmer* involved a method for determining the risk of fetal Down's syndrome by measuring screening markers and comparing the marker levels with an empirical frequency distribution of the markers in affected and unaffected pregnancies.[144] Without an additional step after determining the correlation, the Federal Circuit characterized the claim as a mental step, and the correlation between marker levels and the risk of Down's syndrome as a law of nature.[145] The "measuring" steps were routine and conventional, thus insufficient to make the claims patent-eligible.[146]

More recently, in *Ariosa*, the Federal Circuit again invalidated similar claims directed to a novel method of detecting cell-free fetal DNA in "maternal plasma or serum to determine fetal characteristics."[147] This invention provided "an alternative for prenatal diagnosis of fetal DNA that avoids the risks of widely-used techniques that took samples from the fetus or placenta."[148] Despite this significant contribution to

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141. *In re* BRAC1- and BRAC2-Based Hereditary Cancer Test Patent Litig. v. Ambry Genetics Corp., 774 F.3d 755, 764–65 (Fed. Cir. 2014).

142. PerkinElmer, Inc. v. Intema Ltd., 496 Fed. Appx. 65 (Fed. Cir. 2012); Ariosa Diagnostics, Inc. v. Sequenom, Inc., 788 F.3d 1371 (Fed. Cir. 2015).

143. *PerkinElmer*, 496 Fed. Appx. at 66.

144. *Id.* at 66–68.

145. *Id.* at 70–71.

146. *Id.* at 71.

147. *Ariosa*, 788 F.3d at 1373.

148. *Id.*

public health, the court ruled that this discovery is a law of nature and application of routine and conventional technique did not tip the balance of patentability.[149] Personalized medicine, as discussed in Section I, requires establishing the correlation of genetic variations with a disease and/or patients' physiological responses to dosage regimens.[150] This demands significant investment in testing, data collection, and analysis; however, *Mayo* and *Myriad* cast grave doubts upon the patentability of the resulting discoveries.

Collectively, *KSR*, *Mayo*, and *Myriad* raised a nearly unobtainable standard for dosage regimen patent protection, even for the pre-personalized medicine era. *Mayo*'s two-part test effectively eliminated most method claims of dosing patents that rely on correlations between drug dosing and patients' responses as a way to optimize dosage regimens,[151] and it delivered the same blow to diagnostic patents based on genomic screening in *Myriad*, unless a novel detection method is used.[152] Furthermore, the Court in *Myriad* declared the genes responsible for certain diseases are not patentable.[153] Even if a dosage regimen is determined for a patient subgroup and deemed patentable subject matter, seeking patent protection on it will then face the high non-obviousness standard in *KSR*.[154]

In the era of personalized medicine, most of the genetic testing and dosage design will be performed outside of the pharmaceutical companies.[155] Even when the companies decide to conduct their own research to determine dosage regimens for subgroups of patients, the methods of dosing will not be

149. *Id.* at 1377–78.

150. *See* sources cited *supra* note 41 and accompanying text.

151. Mayo Collaborative Servs. v. Prometheus Lab., Inc., 132 S. Ct. 1289, 1299–1300 (2012) (suggesting that the patent merely states the steps necessary to apply a law of nature and tells doctors to "apply it").

152. Ass'n for Molecular Pathology v. Myriad Genetics, Inc., 133 S. Ct. 2107, 2112–13 (2013) (discussing the techniques used in Myriad's patents).

153. *Id.* at 2119–20.

154. KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398, 420, 428 (2007); *see* 35 U.S.C. §§ 101, 103 (2012) (requiring that, in order to receive a patent, the invention must satisfy non-obviousness grounds of § 103 and patentable-subject matter grounds of § 101, separately).

155. See *supra* note 119 and accompanying text.

patentable under *Mayo*.[156] Dosage regimens themselves are in theory patentable, but overcoming *KSR* will require some rather unexpected results. Given how most researchers will be using similar next-generation sequencing technologies to test a patient for an optimized dosage regimen, it would be hard not to fall into the "obvious to try" or "using a technology to solve a similar problem" category.[157] In light of these developments in patent law, technological development, and advancing medical practice, dosage regimen patents will decline in number and significance. Therefore, pharmaceutical companies need to seek alternative strategies to maintain their competitive edge in the market.

C. POSSIBLE STRATEGIC RESPONSES TO THE CHALLENGE OF DOSAGE REGIMEN PATENTS IN THE ERA OF PERSONALIZED MEDICINE

1. Recommendation 1: Continue seeking patent protection.

"The pharmaceutical industry is one of three technology-based industries in which the patent virtually equals the product. Since capital investment in the pharmaceutical industry disproportionally is directed to . . . research and clinical trials . . . patent exclusivity is the only effective way to protect and receive a return on that investment."[158] Therefore, the first recommendation focuses on strategies to help navigate the current jurisprudence of dosage regimen patents.

Novel Detection/Measurement Methods: The Supreme Court stated in *Mayo* "[p]urely 'conventional or obvious' '[pre]-solution activity' is normally not sufficient to transform an unpatentable law of nature into a patent-eligible application of such a law."[159] Thus, a method for diagnosing disease A by detecting the presence or absence of a biomarker B will most likely be rendered unpatentable subject matter unless the invention uses unconventional or novel detection platforms. For example, say biomarker B is being measured with a new

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156. *Mayo*, 132 S. Ct. at 1299–1300; *see also* sources cited *supra* note 125 and accompanying text.

157. *See KSR*, 550 U.S. at 417, 421.

158. Bruce Lehman, *The Pharmaceutical Industry and the Patent System*, WAKE FOREST U. 7 (2003), http://users.wfu.edu/mcfallta/DIR0/pharma_patents.pdf.

159. *Mayo*, 132 S. Ct. at 1298.

antibody or a novel fluorescent tag. This scarifies the scope of the original claim in exchange for passing the *Mayo* test. When choosing this strategy, the strength and novelty of the new detection method plays a large role in generating value for the claim.

Additional Steps: The second step of the *Mayo* test requires additional elements to "transform the nature of the claim" into a patent-eligible application.[160] In *Classen*, the claim appended a physical administration step after the diagnostic step and successfully converted an abstract diagnostic test to a patentable application.[161] The patent was directed toward "[a] method of immunizing a mammalian subject," which is comprised of a screening step followed by an immunization step in which the subject was physically immunized based on the results.[162] The Federal Circuit held that the addition of this physical step "moves the . . . claims through the coarse filter of § 101 . . . from principle to application."[163] This method may have enforceability limitations that will be discussed in *Recommendation 2*. Alternatively, a step can be added to create a non-natural, man-made product or intermediate that is detected instead of the biomarker itself. For example, a chemical tag can be used to react with the biomarker and then resulting complex will be measured through conventional methods as an indicator for the disease. Since a man-made complex is generated, it can arguably satisfy § 101.

Other possibilities: Adjudicated cases so far have only addressed the patentability of one biomarker/one disease correlation. It is unclear whether the detection of multiple biomarkers (A, B, and C) to diagnose one or more concurrent diseases would pass § 101. A strict reading of the *Mayo* test would still render it a law of nature, but a creative use of a biomarker combination might qualify it as an unconventional or non-routine detection approach.

In the meantime, after the denial of an en banc hearing from the Federal Circuit, a petition for certiorari was filed with the U.S. Supreme Court to revisit the *Mayo* test as applied in

160. *Id.* at 1297.

161. Classen Immunotherapies, Inc. v. Biogen IDEC, 659 F.3d 1057, 1065 (2011).

162. *Id.* at 1060–61.

163. *Id.* at 1068.

the *Ariosa* case.[164] Echoing Judge Linn's concurrence in *Ariosa*, academic and professional commentators urged the Court to distinguish the new discovery in *Ariosa* with the well-known correlation in *Mayo* and reexamine the sweeping language in the precedent.[165] If the Court decided to grant certiorari, it could "possibly [be] the biggest challenge to patent eligibility since . . . [the] *Bilski v. Kappos*" decision in 2010,[166] and the recommendations elaborated in this note would need to be adjusted accordingly.

2. Recommendation 2: Pursue patent rights cautiously and seek collaboration with hospitals or independent laboratories.

As discussed above, the Supreme Court precedents limit dosage regimen patents to narrow instrument-, method-, or drug-specific claims.[167] Assuming valuable dosage regimen patents are obtainable in the current judicial environment, this recommendation focuses on the enforceability of these rights in the era of personalized medicine and advocates for pharmaceutical companies to seek more proactive collaborations with medical facilities.

Regardless of the eventual outcome in *Ariosa*, two components are necessary in personalized medicine: a genetic testing step to determine dosage regimen and a drug administration step. The nature of this approach may raise concerns as to who will be the inventor/owner of the first step, and whether these patents are enforceable if the two steps are performed by separate entities. Turning genetic information into actionable medical decisions requires testing of a large number of patients, data collection, and analysis to establish the correlation between the patient's genetic variations and effective dosage regimens.[168] We have also come to the conclusion that this correlation alone would not be enough to

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164. Hal Wegner, *Top Ten No. (1) Patent Case: Sequenom v. Ariosa at the Supreme Court*, L.A. INTELL. PROP. L. ASS'N (Dec. 7, 2015), http://www.laipla.net/top-ten-no-1-patent-case-sequenom-v-ariosa-at-the-supreme-court/.

165. Paul Cole, *Guest Post: Ariosa v Sequenom—A Path to the Supreme Court?*, PAT. DOCS BLOG (Dec. 14, 2015), http://www.patentdocs.org/2015/12/guest-post-ariosa-v-sequenom-a-path-to-the-supreme-court.html.

166. Wegner, *supra* note 164.

167. *See supra* Part II.B.

168. Myers, *supra* note 56, at 14–15.

pass the § 101 test.[169] Consequently, to retain patent rights in dosage regimens, the pharmaceutical companies would have to invest significantly to invent both components and draft two-step claims to cover both dosage regimen determination and drug administration parts. Alternatively, they could choose to pursue only composition patents on new chemical entities and leave the diagnostic and administration steps to medical professionals or others. However, before choosing one option over the other, we need to take a close look at the enforceability of two-step claims in the context of personalized medical practice.

Doctor/Independent Laboratory: Following an initial diagnosis, an oncologist takes a blood sample from his or her patient and sends it to an independent laboratory for whole genome sequencing. The laboratory then tests the genetic variations and transmits the results back to the hospital, where the doctor makes the dosage regimen decisions accordingly and administers medications to the patient. To infringe the patentee's two-step patent directly or indirectly, all steps in the claim have to be completed by one entity,[170] and in our scenario, one party has to be conducting the genetic test, determining the dosage regimen, and administrating the drugs. However, the doctor and independent laboratory together perform these steps,[171] while neither has done all by itself; thus, there will be no infringement directly or indirectly. It is unlikely the court will find an agency relationship between the hospital and the laboratory, since they do not have controls over the other's actions.[172] Therefore, a two-step patent will be hard to enforce in this scenario.

Doctor/Laboratory in One Hospital: The oncologist takes a sample from the patient and sends it for genetic testing in a laboratory down the hall in the same hospital. The doctor gets

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169. *See supra* Part II.B.

170. *See* Limelight Networks, Inc. v. Akamai Techs., Inc., 134 S. Ct. 2111, 2115 (2014) (holding that "a defendant may [not] be liable for inducing infringement of a patent . . . when no one has directly infringed the patent . . . .").

171. The patient may be performing part of the steps as well, depending on how the claims are drafted.

172. Akamai Techs., Inc. v. Limelight Networks, Inc., 629 F.3d 1311, 1321 (2010) ("[T]here is no indication that an agency relationship arises when one party simply provides direction, no matter how explicit, to another party. All the elements of an agency relationship must be present.").

the results and determines the optimal dosage regimen for the patient, who later is administered the medication. Patentee, in this case, is able to sue the hospital, the doctor and the laboratory, arguing that the doctor and laboratory are acting as agents for the hospital or under contractual obligations to perform steps of the claim.[173] Although the doctor or laboratory can characterize themselves as independent contractors, the Federal Circuit expressly stated "[a] party that engages another to perform a step of a claimed method as its agent cannot escape liability [for patent infringement] simply by designating its agent an independent contractor if all the elements that otherwise reflect an agency relationship are present."[174]

In light of the enforceability landscape of two-step patents, should pharmaceutical companies obtain a sole composition patent on their new drugs or risk investing billions of dollars to further pursue personalized dosage regimens inventions and patents? There are several factors to take into consideration when making this determination. First, the medical complexity of the disease will affect the cost-benefit analysis of the personalized dosage development. The high cost of drug development is disproportionally devoted to research and clinical trials.[175] Therefore, the extra expenses in additional research efforts of developing personalized dosage regimens must be evaluated in light of the market exclusivity they can generate. For example, in cases where the drugs under development are effective for treating most of the genetic subgroups or the dosage regimens are not drastically different across subgroups, the cost can be reduced to a level that justifies the extra capital.

Secondly, the access to diverse patients is becoming more and more important in developing these genetic traits/drug response correlations. In the "one size fits all" era, the clinical trial sets criteria for patient sample selections such as age, gender, disease stage, and medical history.[176] Unlike these

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173. *Id.* at 1320 ("[T]here can only be joint infringement when there is an agency relationship between the parties who perform the method steps or when one party is contractually obligated to the other to perform the steps.").

174. *Id.*

175. Lehman, *supra* note 158.

176. *Learn About Clinical Studies*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/about-studies/learn (last updated Dec. 2015).

parameters, genetic variations cannot be selected prior to actual testing, significantly increasing the uncertainty and costs of such efforts. Therefore, having access to diverse patients is paramount to having sufficient clinical data for determining dosage regimen correlation.

Moreover, the structure of the genetic testing industry will influence the enforceability of these dosage regimen patents. Currently, in terms of clinical testing revenue, hospital laboratories account for approximately sixty percent while independent laboratories represent thirty-five percent.[177] They are both expected to "grow at the same rate and [be] consistent with [the] overall clinical testing market growth" in the next five years.[178] According to our analysis of the two scenarios above, the patentee can enforce the two-step patents about sixty percent of the time. Finally, alternative means of exclusivity, such as FDA regulations and non-patent intellectual property rights, need to be considered. These will be discussed in the next section.

To minimize these uncertainties and risks, collaboration with hospitals or independent laboratories is worth exploring. Delegating the dosage regimen design to medical facilities or even testing centers could significantly decrease pharmaceutical development costs, freeing up funds for more horizontal research silos to investigate new chemical entities. Additionally, most pharmaceutical companies are using advertisements and government registries to seek potential clinical trial participants.[179] Hospitals and independent laboratories will provide even more access to first-hand data on patients' response to drugs and their feedback on individualized dosage regimens.

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177. CLINICAL LAB. MGMT. ASS'N THINKLAB, WASH. G-2 REPORTS ADVISORY SERVS., LABORATORY INDUSTRY OUTLOOK 2010–2011 4 (2010), https://c.ymcdn.com/sites/www.clma.org/resource/resmgr/Professional_Development_-_Past_ThinkLabs/305_Stephanie_Murg.pdf.

178. *The Future for Hospital and Independent Labs in the U.S. Clinical Testing Market*, *supra* note 21.

179. *See, e.g.*, *Clinical Trials*, AVANIR PHARMACEUTICALS, http://www.avanir.com/products/clinical-trials (last visited Feb. 22, 2016); CLINICAL TRIALS.GOV, https://clinicaltrials.gov/ct2/home (last visited Feb. 28, 2016) (providing a search tool for completed and ongoing clinical trials).

3. Recommendation 3: Seek non-patent exclusivity.

To incentivize continuing innovation, the FDA has implemented numerous provisions to extend market exclusivity; this non-patent exclusivity allows pharmaceutical companies to market their products without competition from generics, gaining significant financial benefits.[180] The Food, Drug, and Cosmetic Act provides four exclusivity opportunities: (1) new chemical entity exclusivity; (2) clinical investigation exclusivity; (3) orphan drug exclusivity; and (4) pediatric exclusivity.[181] A pharmaceutical manufacturer can claim new chemical entity exclusivity by introducing a new active moiety.[182] Additionally, it can receive clinical investigation exclusivity by conducting additional clinical trials for new dosage formulations[183] and new indications, or change from prescription to over-the-counter. Development of orphan drugs, those intended to treat diseases and conditions that affect 200,000 or less Americans, can afford the manufactures with seven years of market exclusivity after FDA approval.[184] Pediatric exclusivity, carrying with it an additional six-month extension, is granted to a sponsor with an approved new drug

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180. *See* FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(b)(2) 3–6 (Oct. 1999), http://www.fda.gov/downloads/Drugs/.../Guidances/ucm079345.pdf; *see also* James R. Copland, *Administrative Compensation for Pharmaceutical- and Vaccine-Related Injuries*, 8 IND. HEALTH L. REV. 277, 286 (2011); Pamela Politis, *Transition from the Carrot to the Stick: The Evolution of Pharmaceutical Regulations Concerning Pediatric Drug Testing*, 12 WIDENER L. REV. 271, 272 (2005).

181. GUIDANCE FOR INDUSTRY: APPLICATIONS COVERED BY SECTION 505(b)(2), *supra* note 180, at 7; Renu Lal, *FDA/CDER SBIA Chronicles: Patents and Exclusivity*, CTR. FOR DRUG EVALUATION & RES.: SMALL BUS. & INDUS. ASSISTANCE 2–3 (May 19, 2015), http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/UCM447307.pdf.

182. Lal, *supra* note 181, at 2.

183. Tracey Walker, *FDA Approves Higher Dose, Less-Frequent Dosing Regimen for Copaxone*, MODERNMEDICINE NETWORK (Jan. 30, 2014), http://formularyjournal.modernmedicine.com/formulary-journal/content/tags/copaxone/fda-approves-higher-dose-less-frequent-dosing-regimen-copaxo; s*ee also* Dose-Response Information to Support Drug Registration, 59 Fed. Reg. 55,972, 55,972–76 (Nov. 9, 1994) (providing guidance for including dose-response information in drug registration applications); Ryan Abbott & Ian Ayres, *Evidence and Extrapolation: Mechanisms for Regulating Off-Label Uses of Drugs and Devices*, 64 DUKE L. J. 377, 377–78 (2014).

184. Lal, *supra* note 181, at 2.

application who conducts a pediatric study in response to a written request from FDA.[185]

Personalized medicine enabled by next-generation DNA sequencing will also raise significant regulatory challenges for the FDA and other federal and state agencies.[186] Ability to quickly adapt to the changes and communicate them effectively will help lower the hurdle to the market and meet consumer needs before competitors emerge.

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185. *Id.*; *see also* Politis, *supra* note 180, at 278 (citing the Food and Drug Administration Modernization Act of 1997).

186. *See* Barbara J. Evans, *The Limits of FDA's Authority to Regulate Clinical Research Involving High-Throughput DNA Sequencing*, 70 FOOD DRUG L. J. 259, 275 (2015) (discussing the right to access variant genetic sequences under the Health Insurance Portability and Accountability Act Privacy Rule); Gail H. Javitt & Katherine Strong Carner, *Regulation of Next Generation Sequencing*, 42 J.L. MED. & ETHICS 9, 9 (Supp. Fall 2014) ("[T]he availability of high-throughput NGS [next generation sequencing] methods has led to a proliferation of potential and actual clinical applications for NGS."); Jessica Elizabeth Palmer, *Genetic Gatekeepers: Regulating Direct-to-Consumer Genomic Services in an Era of Participatory Medicine*, 67 FOOD & DRUG L. J. 475, 488 (2012) ("[P]articipatory models offer certain benefits: reduced costs, quicker subject recruitment, and more avenues for individuals with rare genetic variations to come forward and bring their information to the attention of the research community." (internal footnote omitted)); Margaret A. Hamburg, Comm'r of Food & Drugs, Nat'l Insts. Health, Optimizing FDA's Regulatory Oversight of Next Generation Sequencing Diagnostic Tests (Feb. 20, 2015) (transcript available at, http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM439974.pdf); Adam Berger & Zivana Tezak, *FDA Taking Genomic Testing to the Next Level*, FDA VOICE (Sept. 8, 2015), http://blogs.fda.gov/fdavoice/index.php/2015/09/fda-taking-genomic-testing-to-the-next-level/ (describing the FDA's regulatory strategy in response to the push for next generation clinical testing); Taha A. Kass-Hout & David Litwack, *Advancing Precision Medicine by Enabling a Collaborative Informatics Community*, FDA VOICE (Aug. 5, 2015), http://blogs.fda.gov/fdavoice/index.php/2015/08/advancing-precision-medicine-by-enabling-a-collaborative-informatics-community/ (addressing the challenges the FDA faces in connection with next generation sequencing and the steps it is taking to assist the industry); *Developing Analytical Standards for NGS Testing*, FOOD & DRUG ADMIN. (Nov. 12, 2015), http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM468521.pdf; *Use of Databases for Establishing the Clinical Relevance of Human Genetic Variants*, FOOD & DRUG ADMIN. (Nov. 13, 2015), http://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM467421.pdf. *But see* Mark A. Rothstein, *Currents in Contemporary Bioethics: The Case Against Precipitous, Population-Wide, Whole-Genome Sequencing*, 40 J.L. MED. & ETHICS 682, 682, 687–88 (2012) (suggesting that, currently, "population-wide, whole-genome sequencing" has negative outcomes).

4. Recommendation 4: Seek non-patent intellectual property rights.

Aligned with the company's business objectives, seeking non-patent intellectual property rights can provide competitive advantages.[187] Trademark law protects marks that identify the source of a product or service, preventing consumer confusion and unfair competition.[188] In the United States, pharmaceutical trademarks are subject to the oversight of two government agencies: the US Patent and Trademark Office (USPTO) and the FDA.[189] During a registration process, the USPTO considers "whether the mark is sufficiently distinctive and [whether] there is a likelihood of confusion."[190] Federal registration of the brand is not mandatory to use or seek protection under the Lanham Act but FDA approval is mandatory.[191] The FDA review is independent of USPTO registration and has a different focus, including "promotional and safety reviews."[192] The FDA evaluates "whether the proposed name is overly fanciful so as to be misleading" as well as database searches for "common errors" and "orthographic/phonological similarities."[193] In addition to brand names, the shape and color of a pill can be protected as trade dress "if they are non-functional and have acquired secondary

187. Robert Cook-Deegan et al., *The Next Controversy in Genetic Testing: Clinical Data as Trade Secrets?*, 21 EUR. J. HUM. GENETICS 585, 587 (2013) ("Policies to reward or require data sharing can prevent some foreseeable problems caused by limited access to proprietary data about the clinical significance of genetic variations."); Roseann B. Termini & Amy Miele, *Copyright and Trademark Issues in the Pharmaceutical Industry—Generic Compliance or Brand Drug Imitating—"Copycat or Compliance"*, 84 PA. BAR ASS'N Q. 34, 36–37, 39–44 (2013).

188. Termini & Miele, *supra* note 187, at 35, 38.

189. Nick de la Torre & Jennifer Theis, *Pharmaceutical Trademarks 2012: United States*, *in* Pharmaceutical Trademarks 2012 – A Global Guide 61 (Trevor Little et al., eds., 3rd ed. 2012), http://www.brinksgilson.com/files/pharma_2012__selection_clearance_and_registration.pdf.

190. *Id.*

191. *Id.*

192. *Id.*; *see also* Steve Anderson et al., *Navigating the Challenges of U.S. Pharmaceutical Trademark Clearance Research*, PHARMACEUTICAL PROCESSING (Apr. 14, 2010, 10:13 AM), http://www.pharmpro.com/article/2010/04/navigating-challenges-us-pharmaceutical-trademark-clearance-research.

193. Torre & Theis, *supra* note 189; *see also* Anderson et al., *supra* note 192.

meaning" (acquired distinctiveness).[194] Pharmaceutical trademarks are challenging and labor intensive to obtain,[195] and the high drug cost still tops the list of health care concerns.[196] Therefore, caution must be used when investing extensively in building pharmaceutical trademarks.

While trademark law protects the goodwill of a business, trade secrets are often used as a method to protect inventions.[197] Interpreting the clinical significance of genetic information depends on access to patients' sequencing results and their clinical information.[198] It incentivizes proprietary genetic test providers to develop privately controlled databases containing information essential to translate genetic variations into personalized treatment plans.[199] Instead of having patents with limited lifetimes, it has become common practice to keep these important databases as trade secrets which could last permanently.[200]

One example is Myriad Genetics' "secret" *BRCA* databases; when a woman receives genetic testing legally from another laboratory, medical professionals will not be able to interpret certain information due to the lack of database access.[201] This strategy has allowed Myriad to remain the dominant *BRCA* testing service, even after some of their key patents were invalidated.[202] Thus, pharmaceutical companies that decide to venture into the personalized medicine realm can learn from the success of Myriad and use trade secrets to protect the correlations between genetic variations and drug responses, which might not pass the patentable subject-matter test after *Mayo*. It is worth noting there has been public outcry against this practice, which argues "proprietary databases may hinder interpretation of genomic data and impede the advance of

194. Termini & Miele, *supra* note 187, at 41.

195. Anderson, *supra* note 192.

196. Matthew Perrone, *Drug Prices Top Americans' List of Health Care Concerns*, ASSOCIATED PRESS (Oct. 28, 2015, 3:44 AM), http://bigstory.ap.org/article/61fcced3f00747b4be8d0f12c039a8db/drug-prices-top-americans-list-health-care-concerns.

197. Termini & Miele, *supra* note 187, at 35.

198. Cook-Deegan, *supra* note 187, at 585.

199. *Id.*

200. *Id.* at 586.

201. *Id.*

202. *Id.* at 586–87.

personalized medicine" and public health.[203] Therefore, policy and legislative changes need close monitoring.

III. CONCLUSION

Pharmaceutical companies have been relying on dosage regimen patents to help them maintain and extend market exclusivity and obtain sufficient profit to recoup investment and fund further research. A dosage regimen is how a drug is administered and is at the core of personalized medicine, which tailors the medical treatment to an individual based on his or her genetic makeup, age, gender, environmental exposure, and so on. With the rapid advances of next-generation DNA sequencing technology, scientists now have unprecedented access and ability to extract whole human genome data from patients, which guides them to prescribe the optimal treatment and/or prevention plan based on their genetic variations.

Consequently, as the personalized medicine era approaches, genetic testing will be performed in hospitals, testing facilities, and even patient homes and then translated to optimal dosage regimen design. This new practice removes much dosage regimen research outside of the pharmaceutical companies, thus diminishing dosage regimen patents, which is already facing tremendous obstacles in light of recent developments in U.S. patent law. This note proposed four recommendations for forward-thinking companies to adjust to these changes and embrace the new era including navigating current patent system, seeking non-patent exclusivity and intellectual property rights domestically and internationally, collaborating with research hospitals, and restructuring research efforts. These recommendations will help pharmaceutical innovators adjust their strategies and embrace new opportunities in the personalized medicine era.

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203. *Id.* at 587.

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