

NOTE

INTERPRETING BIOLOGICAL SIMILARITY: ONGOING CHALLENGES FOR DIVERSE DECISION MAKERS

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Similarity is an elusive and complicated concept facing comparisons of biological molecules, as even minute changes to a molecule's structure can dramatically affect its function in the body. Yet the flood of biologic drugs on the market will increasingly force these similarity comparisons. These concerns are particularly relevant to two groups of drugs: families of biologic drugs that closely resemble each other in structure and function, here termed "similar-impact biologics," and the biosimilars, which are intended to closely approximate generic forms of biologic drugs. In bringing biologic drugs to the market, manufacturers are likely to face dual obstacles: FDA approval and patent protection. These hurdles are somewhat in tension with each other. The more similar biosimilars are to their pioneer counterparts, the more easily they may advance to market via the Biologics Price Competition and Innovation Act's ("BPCIA") new accelerated approval pathway. While the FDA has provided some guidance about how much similarity is likely to suffice, the standard is not yet clearly defined. In contrast, the more similar two drugs are to one another, the less likely that they will be able to obtain patent protection. Further, biologic drugs pose special issues when considering various legal factors required for patentability. Resolving these questions for the optimal benefit of all stakeholders requires both fundamental institutional competency and a willingness on the part of decision makers to engage with difficult scientific questions. This Note explores these ongoing challenges, with particular focus on the clinical and litigation history of the TNF α inhibitors Humira, Enbrel, and Remicade.

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INTRODUCTION 424

I. SIMILAR-IMPACT BIOLOGICS AND THEIR CHALLENGES: A CASE STUDY OF THE TNF α INHIBITORS 429

 A. *Defining Drug Similarity* 429

 B. *TNF α Inhibitor Litigation* 433

II. INTERPRETING BIOLOGICAL SIMILARITY: FDA AS DECISION MAKER 435

 A. *The FDA and Biological Similarity* 435

 1. Equivalence Assessments of Small-Molecule Drugs 435

 2. Separate Procedural Consequences for Small-Molecule Drugs and Biologics 436

 3. A New Challenge: Defining the Highly Similar Biologic 438

 B. *Making the Decisions: A Role for Experts* 441

 C. *Making the Decisions: A Role for Postmarket Safety Data* 443

III. INTERPRETING BIOLOGICAL SIMILARITY: PATENT LAW AS DECISION MAKER 445

 A. *Hurdles to Biologic Patentability* 446

 B. *Defining Biologic Obviousness* 448

 C. *Defining Biologic Equivalence* 453

 D. *Expanding the Role of Regulatory Guidance* 455

 E. *Making the Decisions: Choices for Manufacturers* 458

CONCLUSION 460

INTRODUCTION

The degree to which two molecules resemble each other can have significant legal and regulatory consequences. Yet defining these boundaries is no easy feat, given the complexity of the subject matter. When faced with the question of defining similarity, choosing the right word for the task can be problematic and is likely to depend on the speaker’s identity. For example, Congress and the Food and Drug Administration (“FDA”) define “drug” one way in the Federal Food and Drug Cosmetic Act (“FDCA”),¹ while medical professionals employ looser terminology.²

1. See 21 U.S.C. § 321(g)(1) (2011) (“The term ‘drug’ means (A) articles recognized in the official United States Pharmacopœia, official Homœopathic Pharmacopœia of the United States, or official National Formulary, or any supplement to any of them; and (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals; and (D) articles intended for use as a component of any article specified in clause (A), (B), or (C).”).

2. E.g., *Definition: Drug*, MEDILEXICON, <http://www.medilexicon.com/medicaldictionary.php?t=26719> (last visited Feb. 2, 2013) (defining “drug” as a “[t]herapeutic agent; any substance, other than food, used in the prevention, diagnosis, alleviation, treatment, or cure of disease”).

If asked to define “drug,” an ordinary layperson might instinctively try to describe a class of chemicals which I refer to as “small-molecule drugs,” and which fall within the FDCA’s definition. In this context, “small” means that the drug’s structure comprises a relatively limited number of atoms,³ with the result that small-molecule drugs have low molecular weight.⁴ Laboratories can create small-molecule drugs using standard chemical synthesis protocols. The standardization of these protocols makes it relatively easy for other manufacturers to replicate generic, essentially identical versions of small-molecule drugs.⁵

Although small-molecule drugs are perhaps the most familiar type of drugs, a new class of drugs is becoming quite prominent in the market and in the practice of medicine. In recent years, pharmaceutical companies have invested significantly in developing biologics, or drugs based on molecules and proteins in our own bodies.⁶ Scholars have long noted this trend,⁷ and, with the recent passage of the BPCIA, it is only expected to continue. One study predicts that by 2015, nearly half of new drug approvals will be biologics.⁸ These drugs represent a significant investment on the part of manufacturers. Due to their complexity, manufacture of these drugs is complicated and development is quite expensive: one estimate places research and development costs for a single biologic drug at \$1.24–\$1.33 billion.⁹ Developing biologics is thus no trivial endeavor, given the steep rates

3. See, e.g., *Small Molecule Versus Biological Drugs*, GENERICS & BIOSIMILARS INITIATIVE (June 29, 2012), <http://www.gabionline.net/Biosimilars/Research/Small-molecule-versus-biological-drugs> (illustrating this principle with the familiar example of aspirin, which is composed of only twenty-one atoms).

4. *Id.*

5. *Id.*

6. E.g., Kevin Grogan, *Pharma Patent Filings Fall amid Shift to Biologics*, PHARMA TIMES (Mar. 21, 2012), http://www.pharmatimes.com/article/12-03-21/Pharma_patent_filings_fall_amid_shift_to_biologics.aspx. But see *Drug Discovery 2.0: Rise of the Biosimilar? Not So Fast*, CURIOUS WAVEFUNCTION (Aug. 22, 2012), <http://wavefunction.fieldofscience.com/2012/08/will-biologics-supersede-small.html> (“[R]umors of small molecules’ deaths are grossly exaggerated.”).

7. Bryan A. Liang, *Regulating Follow-on Biologics*, 44 HARV. J. ON LEGIS. 363, 363–64 (2007) (“[S]ales of biologics have grown . . . rapidly, with an increase of seventeen percent in 2005 and annual expenditures worldwide of greater than \$50 billion. By 2010, spending on biologics is estimated to grow to \$105 billion, with biologics making up nearly half of all newly approved medicines.”).

8. Berkowitz et al., *Analytical Tools for Characterizing Biopharmaceuticals and the Implications for Biosimilars*, 11 NATURE REVIEWS DRUG DISCOVERY 527, 527 (2012) (also predicting an increase to 70% by 2025).

9. Henry Grabowski, *Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition*, 7 NATURE REVIEWS DRUG DISCOVERY 479, 482 (2008).

of drug failure in clinical trials.¹⁰ Despite the high price tag on biologics,¹¹ however, the risk may well be worth the reward.

Biologic drugs are typically either antibodies or recombinant versions of proteins occurring naturally in the human body (“endogenous proteins”), and the FDA defines them separately from “drugs.”¹² Biologics are purposely designed to share common physical features and properties with endogenous molecules and, in consequence, should be expected to perform essentially the same function in the body as endogenous molecules. If competing pharmaceutical manufacturers independently develop biologic therapeutics against a particular molecular target, it is quite likely that these distinct drugs will share common features and properties. While biologics should closely resemble endogenous molecules or parts thereof, however, they may also have artificial structural features or elements.

Biologics differ from small-molecule drugs in several key aspects. When compared with small-molecule drugs, biologics are quite large.¹³ Although the structure of biologic drugs varies widely, the overall size difference between small-molecule drugs and biologics is likely to be several orders of magnitude. Another essential difference between biologics and small-molecule drugs is the means required to produce them. Like the proteins they are designed to mimic, biologics are necessarily produced by cells, typically either human or animal cells. Due to the high variability of cells, it is impossible to ensure that their protein products are perfectly identical, raising important manufacturing concerns.¹⁴

Thus, the question of what makes different types of drugs “similar” is extraordinarily challenging, and the answer may be quite different for bio-

10. See, e.g., Joseph DiMasi & Henry Grabowski, *Economics of New Oncology Drug Development*, 25 JOURNAL OF CLINICAL ONCOLOGY 209, 212 (2007), available at <http://jco.ascopubs.org/content/25/2/209.full.pdf+html> (finding that approximately half of oncology drugs in expensive Phase III clinical trials failed to gain FDA approval, and that one out of five oncology drugs that entered the approval pipeline process between 1993 and 2002 actually gained approval).

11. See *Small Molecule*, *supra* note 3. Biologics are far more expensive than small molecule drugs and generics.

12. 42 U.S.C. § 262(i)(1) (2011) (“The term ‘biological product’ means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product . . . applicable to the prevention, treatment, or cure of a disease or condition of human beings.”). The Centers for Biological Evaluation and Research (“CBER”) and for Drug Evaluation and Research (“CDER”) of the FDA regulate a wide variety of biological products. See *FDA 101: Regulating Biological Products*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048341.htm#WhatbiologicalproductsdoesFDAregulate> (last updated July 25, 2008). For the purposes of this Note, my analysis concerns the types of drugs regulated by CDER, which include monoclonal antibodies, cytokines, growth factors, enzymes, and immunomodulators.

13. See *Small Molecule*, *supra* note 3 (noting that a “typical monoclonal antibody” is constructed of approximately 20,000 atoms).

14. See discussion *infra* Part II.A.

logics and small-molecule drugs, as this Note will discuss. In contrast, the approach to answering the question may be quite similar for both. One may undertake an atom-by-atom comparison of two drugs in order to determine whether they are structurally similar. Alternatively, one may compare the physiological effect of two drugs by measuring their effect on a particular cellular pathway or molecular target to determine whether they are functionally similar.

In order to tackle the complexity of biological similarity, it is first essential to set forth a realistic classification rubric for biologic drugs and precisely define the terms presently used to describe their constituents. For reasons discussed above, it is impossible to create a true generic version of a biologic. According to the FDA, a generic small-molecule drug is “chemically identical” and “bioequivalent” to a brand-name drug, terms that encompass a wide range of the drug’s biochemical features.¹⁵ The closest and most generic-like approximations of biologics are called “biosimilars” or “follow-on biologics.”¹⁶ As discussed further in Part II, “biosimilar” is a regulatory term, subject to the FDA’s finding that a new biologic is “highly similar” to a preexisting “pioneer” or “reference” biologic already on the market, in the generic manufacturer’s hope that it will function as a generic version thereof.¹⁷ Like the makers of small-molecule generics, biosimilar manufacturers can benefit from an accelerated FDA approval process, explained in Part II.A.3.

A third term generally used to describe drugs—perhaps applicable to biologic drugs that are similar yet not perfectly identical—is “me-too” drugs (“MTDs”). Popular sources of MTD definitions conflict with each other¹⁸ and with the legal description.¹⁹ These inconsistent, “catch-all” definitions

15. See *FDA Generic Drugs: Questions and Answers*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm100100.htm> (last updated Aug. 24, 2011) (“A generic drug is identical—or bioequivalent—to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. . . . FDA requires generic drugs have the same high quality, strength, purity and stability as brand-name drugs.”).

16. See Liang, *supra* note 7, at 399. Although the U.S. originally adopted the term “follow-on biologics,” “biosimilar” is also now commonly used.

17. See, e.g., *Market Opportunities for Biosimilars*, GENERICS & BIOSIMILARS INITIATIVE (June 17, 2011), <http://www.gabionline.net/Biosimilars/General/Market-opportunities-for-biosimilars> (anticipating \$2 billion to be spent on biosimilar development by 2015, mainly due to significant patent expiries of the pioneer biologics).

18. Compare, *Me Too Drug*, FREE DICTIONARY, <http://medical-dictionary.thefreedictionary.com/me+too+drug> (last visited Feb. 16, 2013) (“A popular term for a generic drug with an identical formulation and stated indications as a previously FDA-approved agent.”), with *Definition of Me-Too Drug*, MEDICINE NET, <http://www.medterms.com/script/main/art.asp?articlekey=33748> (last visited Feb. 16, 2013) (“A drug that is structurally very similar to already known drugs, with only minor differences.”).

19. See *USV Pharm. Corp. v. Richardson*, 461 F.2d 223, 228 n.15 (4th Cir. 1972) (“A ‘me-too’ drug is generally defined as ‘one which is equivalent to another, pioneer drug, which preceded it on the market.’” (citing Note, *Drug Efficacy and the 1962 Drug Amendments*, 60

may stem from a general difficulty with defining this group in a precise way. The MTD label is commonly applied to small-molecule drugs, and it is unclear whether the term “biosimilar” will come to be interchangeable with “me-too” in the context of biologics. Biosimilarity requires “high” similarity defined by the FDA, while the MTD label implies a more indeterminate level of equivalence. A fourth classification of biologic drugs termed “bio-betters”²⁰ are therapeutics created when a manufacturer takes a reference drug and alters its structure in a way that improves its function or performance in the body.²¹ Although brief, these descriptions of biosimilars, MTDs, and bio-betters should indicate that the drugs in these groups have a high degree of structural similarity to pioneers.

A fifth possible classification of biologic drugs includes biologics that are functionally similar, but unlike the previous class of drugs, they may or may not be structurally similar. These biologics have the same molecular target or may act to affect the same cellular processes so that physicians can use them to treat the same disease. In the interest of promoting as much clarity as possible, this Note refers to drugs falling into this classification scheme as “similar-impact biologics,” although there may be conceptual overlap with the MTD definition.

The groups listed above merely illustrate a possible way to classify drugs based on the extent of their structural resemblance, underscoring that defining biologic similarity is extraordinarily complicated. As this Note will discuss, the answer varies among different institutions and agencies, as in the course of the drug approval process or patent infringement litigation, various agencies often must evaluate one drug’s similarity to other drugs at both a structural and functional level. In these evaluations, they may undertake an atom-by-atom comparison of two biologics in order to determine whether they are structurally similar. Alternatively, they may compare the physiological effect of two biologics by measuring their effect on a particular cellular pathway or molecular target to determine whether they are functionally similar.

These determinations can be a double-edged sword. As described below, in the case of market approval by the FDA, similarity to a drug already on the market can accelerate a generic therapeutic’s approval, but such similarity can also create problems for obtaining and retaining a patent, as decided

GEO. L. J. 185, 198 n. 78 (1971)), *aff’d sub nom.* USV Pharm. Corp. v. Weinberger, 412 U.S. 655 (1973).

20. See *Biobetters Rather than Biosimilars*, GENERICS & BIOSIMILARS INITIATIVE (June 5, 2011), <http://www.gabionline.net/Biosimilars/General/Bio-betters-rather-than-biosimilars> (“The enhancement [effect of bio-betters] may range from better efficacy, or a longer half-life, allowing for a lower dosing frequency and reduced risk of immunogenicity, to lower toxicity and reduced side effects.”).

21. See, e.g., *Biobetters Q&A*, BIORESEARCH ONLINE (Sept. 7, 2011), <http://www.bioresearchonline.com/doc.mvc/Bio-betters-QA-0001>.

by the US Patent and Trademark Office (“USPTO”). Further, these agencies are not the final word, and courts may get involved. Thus, biological similarity from a legal perspective may be evaluated quite differently, depending on the decision maker.

This Note explores how the regulatory and patent systems currently handle complicated questions of biological similarity. Part I focuses on a family of similar-impact biologic drugs as a case study to illustrate regulatory and litigation challenges facing similar biologic and biosimilar development. Part II describes the mechanics of biologic drug approval and discusses the FDA’s approach to similar drugs. Part III reviews selected areas of patent law where biological similarity is of key importance and highlights instances of disconnect between patent law and the FDA.

I. SIMILAR-IMPACT BIOLOGICS AND THEIR CHALLENGES: A CASE STUDY OF THE TNF α INHIBITORS

A. Defining Drug Similarity

Perhaps the most prominent family of similar biologic therapeutic molecules presently available on the market is the tumor necrosis factor alpha (“TNF α ”) inhibitors. These drugs interfere with the biological activity of TNF α and act as immunosuppressants. To briefly summarize a complicated signaling network, activated macrophages secrete TNF α into the body’s extracellular milieu, where it recognizes and binds a variety of target receptors (“TNFRs”) expressed on the surface of cells. TNF α ’s bioactivity is nuanced: TNF α -TNFR binding activates molecular signaling pathways inside the cell, which can ultimately turn on expression of genes that either mediate inflammation or induce cellular death.²² Pathological dysregulation of TNF α signaling is implicated in diseases as diverse as rheumatoid arthritis,²³ chronic plaque psoriasis, Crohn’s disease (inflammatory bowel syndrome), and cancer.

The three market-dominant TNF α inhibitors are Pfizer’s Enbrel (etanercept), Abbott Laboratories’ Humira (adalimumab), and Remicade (infliximab), produced by Centocor (a Johnson & Johnson subsidiary) and Schering-Plough, among other assignees. These drugs exert their effects through conceptually similar mechanisms. Enbrel is a soluble fusion protein

22. See, e.g., Lucia Cabal-Hierro & Pedro S. Lazo, *Signal Transduction By Tumor Necrosis Factor Receptors*, 24 CELL SIGNALING 1297 (2012); Thomas Helgans & Klaus Pfeffer, *The Intriguing Biology of the Tumour Necrosis Factor/Tumour Necrosis Factor Receptor Superfamily: Players, Rules and the Games*, 115 IMMUNOLOGY 1, 2 (2005) (“[I]t became apparent that most members of the TNF superfamily interact with more than one receptor [Later] it was possible to define the physiological function linked to individual ligands or receptors in more detail and it became clear that almost each receptor-ligand system of this TNF/TNFR superfamily appears to have a unique and non-redundant function.”).

23. Bharat B. Aggarwal et al., *Historical Perspectives on Tumor Necrosis Factor and Its Superfamily: 25 Years Later, a Golden Journey*, 119 BLOOD 651, 660 (2012).

based on the TNF receptor. In the body, it acts as a competitive inhibitor of TNF α -TNFR signaling via binding TNF α and preventing it from interacting with its target receptor. By comparison, Humira and Remicade are human- and mouse-derived monoclonal antibodies,²⁴ respectively, that bind to the TNF α molecule to block TNFR interaction. Thus, although Remicade and Humira structurally resemble each other, but not Enbrel, all three molecules act in a similar fashion. Importantly for the industry, these biologics are each huge moneymakers—one analysis placed all three in the top four best-selling drugs of 2012²⁵—generating over \$6 billion in sales that year.²⁶ Unsurprisingly, competition for market dominance is fierce.²⁷

These three drugs each interfere with the same target, and recent data indicate a statistically similar mortality rate when administered to patients.²⁸ Their biological activity is not identical, however. This finding is illustrated in clinical studies of the TNF α inhibitors' effect on rheumatoid arthritis ("RA"), an autoimmune disease characterized by joint pain and degeneration, and upon which most TNF α inhibitor research has focused. The findings of these studies can be broken down into two major points: drug efficacy and relative safety.

The first point for comparison is drug efficacy: that is, how much is required to have the desired therapeutic effect. In a four-year study of RA patients taking one of the three drugs, patients stayed on Enbrel significantly longer than on either Humira or Remicade.²⁹ Perhaps not coincidentally, a comparative effectiveness study found that RA patients taking Enbrel were less likely to escalate their dose than patients on Humira and Remicade,³⁰ as dose escalation implies that patients have become nonresponsive to the drug at lower doses. Similarly, Swiss researchers observed that patients developed

24. That is, antibodies that only recognize one site (or "epitope") on a particular protein.

25. John D. Carroll, *The 15 Best-Selling Drugs of 2012*, FIERCEPHARMA (Oct. 9, 2012), <http://www.fiercepharma.com/special-reports/15-best-selling-drugs-2012>.

26. Rodney J.Y. Ho & Jenny Y. Chien, *Drug Delivery Trends in Clinical Trials and Translational Medicine: Growth in Biologic Molecule Development and Impact on Rheumatoid Arthritis, Crohn's Disease, and Colitis*, 101 J. PHARMACEUTICAL SCI. 2668 (2012), available at <http://www.ncbi.nlm.nih.gov/pubmed/22573521>.

27. *Abbott/Eisai's Humira has Emerged as Leading Psoriasis Agent*, PHARMALETTER (Aug. 7, 2012), <http://www.thepharmaletter.com/file/115519/abbotteisais-humira-has-emerged-as-leading-psoriasis-agent.html>.

28. See Julia F. Simard et al., *Mortality Rates in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: Drug-Specific Comparisons in the Swedish Rheumatism Register*, 64 ARTHRITIS & RHEUMATISM 3502 (2012).

29. Florenzo Iannone et al., *Longterm Retention of Tumor Necrosis Factor- α Inhibitor Therapy in a Large Italian Cohort of Patients with Rheumatoid Arthritis from the GISEA Registry: An Appraisal of Predictors*, 39 J. RHEUMATOLOGY 1179, 1179 ("The mean duration of therapy was significantly longer for etanercept (3.1 ± 2 yrs) than for adalimumab (2.6 ± 2 yrs) or infliximab (2.7 ± 2 yrs; $p < 0.05$).").

30. Vernon F. Schabert et al., *Disability Outcomes and Dose Escalation with Etanercept, Adalimumab, and Infliximab in Rheumatoid Arthritis Patients: A US-Based Retrospective Comparative Effectiveness Study*, 28 CURRENT MED. RES. & OPINION 569 (2012).

resistance to Remicade more quickly than to Humira or Enbrel.³¹ They also noted a reduction in therapeutic response after the first six months of Remicade therapy, a finding that was not observed with the other two drugs.³² A Danish study found that Remicade had the lowest rate of disease remission and drug adherence, whereas treatment with Humira led to the best clinical outcome.³³ When solely compared with Enbrel, however, Remicade appears to be more effective at preventing joint damage in RA patients.³⁴

Other comparative analyses of the TNF α inhibitors have focused on their relative safety.³⁵ In the Danish study, Enbrel recipients demonstrated the longest survival rates,³⁶ and a subsequent meta-analysis of the literature on TNF α inhibitors suggested that Enbrel might be the safest alternative.³⁷ Specifically, the authors of that study noted that RA patients on Humira and Remicade were more likely to discontinue the use of the drug due to an adverse effect³⁸ than were patients on Enbrel.³⁹ One French study found an elevated risk of lymphoma in RA patients using the monoclonal antibody therapeutics when compared to either Enbrel users or the population as a whole,⁴⁰ and Humira and Remicade have been associated with increased risk of other diseases as well.⁴¹ These studies provide a sufficient picture of rela-

31. See A. Finckh et al., *Evidence for Differential Acquired Drug Resistance to Anti-Tumour Necrosis Factor Agents in Rheumatoid Arthritis*, 65 ANNALS OF RHEUMATIC DISEASES 746, 746 (2006) (finding significantly elevated requirements for co-therapy and dose escalation for Remicade only, and no significant treatment discontinuation between drugs).

32. *Id.*

33. See Merete Lund Hetland et al., *Direct Comparison of Treatment Responses, Remission Rates, and Drug Adherence in Patients with Rheumatoid Arthritis Treated with Adalimumab, Etanercept or Infliximab: Results from Eight Years of Surveillance of Clinical Practice in the Nationwide Danbio Registry*, 62 ARTHRITIS & RHEUMATISM 22 (2010).

34. See Axel Finckh et al., *The Effectiveness of Anti-Tumor Necrosis Factor Therapy in Preventing Progressive Radiographic Joint Damage in Rheumatoid Arthritis: A Population-Based Study*, 54 ARTHRITIS & RHEUMATISM 54 (2006) (finding a statistically significant difference [$p = 0.02$] when comparing disease progression in patients treated with antirheumatic drug therapy plus either Enbrel or Remicade).

35. See Daniel E. Furst et al., *Open-Label, Pilot Protocol of Patients with Rheumatoid Arthritis Who Switch to Infliximab After an Incomplete Response to Etanercept: The Opposite Study*, 66 ANNALS RHEUMATIC DISEASE 893 (2007), reviewed by Axel Finckh, *Comparative Effectiveness of Rheumatoid Arthritis Therapies*, 12 CURRENT RHEUMATOID REPORTS 348 (2010).

36. Hetland et al., *supra* note 33, at 28 fig. 3.

37. Kalle J. Aaltonen et al., *Systematic Review and Meta-Analysis of the Efficacy and Safety of Existing TNF Blocking Agents in Treatment of Rheumatoid Arthritis*, PLoS ONE, Jan. 2012, at 1.

38. See *What Is a Serious Adverse Event*, FOOD & DRUG ADMIN. (June 23, 2011), <http://www.fda.gov/safety/medwatch/howtoreport/ucm053087.htm>.

39. Aaltonen et al., *supra* note 37, at 7 tbl. 3.

40. X. Mariette et al., *Lymphoma in Patients Treated with Anti-TNF: Results of the 3-Year Prospective French RATIO Registry*, 69 ANNALS RHEUMATIC DISEASE 400 (2010).

41. See Finckh et al., *supra* note 34, at 351 (discussing an increased risk of tuberculosis and herpes zoster with use of the monoclonal antibody therapeutics).

tive clinical efficacy and safety to enable an observer to distinguish between these drugs, despite their similarity.

The big-picture cohort studies described above provide essential data for decision making on the part of patients, doctors, regulatory agencies, and the pharmaceutical industry, but they are not the only source of pertinent information. Single-patient case studies also improve our understanding of the kind of nuanced biological response that is likely to differentiate similar drugs. One case study of an RA patient reported differences in liver responses to sequential treatment of Enbrel, Humira, and Remicade.⁴² The patient's serum aminotransferase levels were elevated when treated with the first two drugs, but normalized when switched to Remicade.⁴³ The authors of the study remarked upon the complexity of liver injury that could result even from treatment by different drugs in the same class of therapeutics.⁴⁴

The takeaway message is that even biologic molecules with similar structure and function—and those with a demonstrated strong safety profile, like the TNF α inhibitors—may have noticeably disparate physiological impact, particularly when the analysis becomes more fine grained. Further, these complications are by no means limited to the TNF α inhibitors. Many individual proteins serve diverse and numerous functions in the cell, a phenomenon termed “moonlighting,”⁴⁵ and the expression of endogenous proteins is tightly regulated to modulate their biological effects.⁴⁶ Thus, using a biologic drug may have unexpected consequences either arising from the drug's interference with cellular targets beyond the one intended for the therapy, or from downstream effects of drug-target interaction. Proteins are also frequently altered following cellular expression, commonly either as a result

42. Jose Carlos Titos-Arcos et al., Letter to the Editor, *Recurrent Hepatotoxicity Associated with Etanercept and Adalimumab but Not Infliximab in a Patient with Rheumatoid Arthritis*, 104 REV. ESP. ENFERM. DIG. 282 (2012), available at <http://www.grupoaran.com/mrm/Update/lecturaPDFfromXML.asp?IdArt=4620244&TO=RVN&Eng=1>.

43. *Id.* at 282.

44. *Id.* at 283.

45. *E.g.*, Constance J. Jeffery, *Moonlighting Proteins*, 24 TRENDS BIOCHEMICAL SCI. 8 (1999). The consequence is that a biologic drug would also impact the same diversity of functions as the molecule it is designed to resemble.

46. *See, e.g.*, S. Thomas Carmichael, *Gene Expression Changes After Focal Stroke, Traumatic Brain and Spinal Cord Injuries*, 16 CURRENT OPINIONS NEUROBIOLOGY 699 (2003) (describing wave-like patterns of gene expression following ischemic brain injury); Samantha N. Greer et al., *The Updated Biology of Hypoxia-Inducible Factor*, 31 EMBO J. 2448 (2012), available at <http://www.nature.com/emboj/journal/v31/n11/full/emboj2012125a.html> (reviewing the role of the HIF1 transcription factor, which is selectively upregulated in hypoxic environments, and which promotes expression of a plethora of pro-angiogenic genes).

of post-translational modifications or proteolysis.⁴⁷ An unrelated area of concern is biologics' ability to trigger an unwanted immune system response.⁴⁸

Thus, even though they resemble endogenous molecules, these general characteristics of biologics raise red flags about their safety. Scholars have noted that this multi-factorial regulation of protein function has significant implications for biosimilar manufacture,⁴⁹ as it may be difficult for manufacturers to control this element of production.⁵⁰ The situation becomes still more complicated when the biosimilars enter into the picture, because they are necessarily different from the pioneer molecule,⁵¹ yet are designed to be "highly similar" to it. Because manufacturers are already working to develop biosimilar versions of some of the TNF α inhibitors, the FDA is certain to face the question of whether these forthcoming drugs merit this label.⁵²

B. TNF α Inhibitor Litigation

The biological similarity between the two monoclonal antibody TNF α inhibitors has led to infringement litigation between their two manufacturers. In 2009, Remicade patent assignee Centocor sued Abbott Laboratories,⁵³ asserting that the Humira patent⁵⁴ infringed several of its claims.⁵⁵

47. Examples of modifications include: glycosylation, phosphorylation, farnesylation, prenylation, myristoylation, and ubiquitination. Proteolysis refers to the cleavage of a substrate protein by an enzyme. This mechanism often yields bioactive fragments from a larger parent molecule.

48. Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition*, B.C. INTELL. PROP. & TECH. F., July 19, 2009, at 12 ("The propensity to become immunogenic is a special concern for large biologics that is generally not problematic for small molecule drugs.").

49. E.g., Liang, *supra* note 7, at 371; Sahr, *supra* note 48, at 11 ("In living cells, the activity of chaperones or other molecules that interact with proteins during synthesis can add variability to the end product.").

50. Trevor Woodage, *Blinded By (A Lack of) Science: Limitations in Determining Therapeutic Equivalence of Follow-on Biologics and Barriers to Their Approval and Commercialization*, 2012 STAN. TECH. L. REV. 9, ¶ 13 (describing the "multi-factorial nature of the manufacturing substrates and methods" used in producing biosimilars); *see also infra* Part III.A.3.

51. *See infra* Part III.A (discussing manufacturing problems of the biologics); Liang, *supra* note 7, at 371 ("Because of the differences in production and size between biologics and chemical drugs, as well as the unique cellular source of biologics, it is nearly impossible to make truly identical copies of a protein using two different production cell lines."). According to Liang and his sources, this impossibility precludes generation of a true generic biologic molecule.

52. *See infra* Part II.A.3 for a discussion of the TNF α biosimilars.

53. Centocor Ortho Biotech, Inc. v. Abbott Labs., 669 F. Supp. 2d 756, 760 (E.D. Tex. 2009) ("[T]he Court finds that Abbott has not proven by clear and convincing [sic] that [Centocor's] patent is unenforceable or invalid."), *rev'd*, 636 F.3d 1341 (Fed. Cir. 2011).

54. U.S. Patent No. 8,197,813 col. 51 l. 2 (filed Mar. 10, 2009) (claiming "[a]n isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNF α (hTNF α) with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of $1 \times 10^{-3} s^{-1}$ or less").

55. U.S. Patent No. 7,070,775 (filed July 18, 2002).

Although structurally similar, Remicade and Humira are distinctly different molecules. Their differences stem from the dissimilar initial creative approaches of their respective manufacturers.⁵⁶ The portion of the Remicade antibody that recognizes TNF α is technically a mouse protein, derived from a mouse exposed to human TNF α . The other portion of the Remicade antibody is a piece of human antibody. This fusion of proteins from different species, termed a “chimera,” prevents an unwanted immune response when Remicade is injected into the human body.⁵⁷ By contrast, Abbott’s Humira is an entirely human antibody, built piecemeal from an existing library of human-derived molecules previously screened for capability to bind TNF α .⁵⁸

In pursuing litigation against Abbott, Centocor argued that Humira’s properties infringed the Remicade patent, despite the structural differences described above. At trial, the jury agreed with Centocor and awarded a \$1.67 billion verdict, one of the largest in patent infringement litigation history.⁵⁹ Given the structural similarity between the two molecules, this outcome may not have been totally surprising. The Federal Circuit subsequently reversed the trial verdict, however, holding that Centocor’s claims to a fully human antibody exceeded the scope of its original written description.⁶⁰ This saga and its sequence of outcomes highlights two issues: it serves as a discrete example of the kinds of biological differences that juries and judges must confront in these cases, and it suggests potential problems with the ability of juries to handle highly technical material, discussed further in Part III.B.⁶¹

While the TNF α inhibitors are only one family of similar-impact biologics, their challenges are informative and potentially representative of what other manufacturers of similar-impact biologics will confront. The same issues are likely to appear for other families of biologics where the molecules have identical targets but very different structural components.

56. *Centocor*, 636 F.3d at 1344, 1346 (“In developing their therapeutic TNF- α antibodies, Centocor and Abbott pursued very different strategies. Centocor’s path began by identifying a mouse antibody to human TNF- α that had both high affinity and neutralizing activity Abbott decided to work with collaborators to construct a fully-human antibody from scratch.”), *cert. denied*, 132 S. Ct. 1542 (2012).

57. *See id.* at 1344–45.

58. *See id.* at 1346.

59. *E.g.*, Bruce Japsen, *Abbott Wins Appeal in \$1.67B Humira Patent Infringement Case*, CHI. TRIB. (Feb. 26, 2011), http://articles.chicagotribune.com/2011-02-23/business/ct-biz-0224-abbott-humira-20110224_1_humira-rheumatoid-arthritis-drug-knoll-pharmaceuticals-abbott-laboratories.

60. *Centocor*, 636 F.3d at 1353. *See infra* Part III.A for an explanation of these terms’ significance.

61. Also see *infra* Part III.D for a discussion of decision making.

II. INTERPRETING BIOLOGICAL SIMILARITY: FDA AS DECISION MAKER

A. *The FDA and Biological Similarity*

Over the past half century, the FDA's duty has been to determine that drugs are safe and effective for market.⁶² With few exceptions,⁶³ the FDA is not required nor encouraged to assess the comparative effectiveness of the drugs it approves.⁶⁴ Despite this fact, the FDA still considers questions of drug equivalence, most significantly in the context of determining whether generic drugs may enter the market. Much of the FDA's interpretive precedent is limited to small-molecule drugs, and the advent of the biosimilars will force the agency to answer the new question of what makes two biologics "highly similar."

1. Equivalence Assessments of Small-Molecule Drugs

How should the FDA handle biologics equivalence? Several statutory and regulatory definitions are possible and will be discussed in this Note. Most definitions derive from the FDA's treatment of small-molecule drugs, and it is unclear how much this reasoning will, or should, carry over into evaluating biological similarity.

First, it is important to note that biologics are different from small-molecule drugs. As described in the Introduction, Congress initially drew a distinction between the FDCA's drug and the Public Health Service Act's ("PHSA") "biological drug," giving each term its special meaning.

The FDA has further elaborated on these definitions, creating analytical frameworks for their assessments. In implementing the Orphan Drug Act, the FDA tackled the question of what makes two drugs "the same" drug.⁶⁵ Significantly, the FDA clearly distinguished between small-molecule drugs⁶⁶

62. See, e.g., *The Food and Drug Administration's Critical Mission and Challenges for the Future Before the H. Comm. on Oversight and Gov't Reform*, 110th Cong. 39–49 (2007) (statement of Andrew C. Von Eschenbach, Comm'r, Food & Drug Admin.).

63. In determining whether two drugs are the "same" under the Orphan Drug Act, see 21 C.F.R. § 316.3(b)(13) (2012) ("[I]f the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug.>").

64. See Robert J. Temple, *Comparative Effectiveness Research*, FOOD & DRUG ADMIN. 2 (Apr. 21, 2010), <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM209270.pdf> ("FDA's experience with comparative effectiveness claims is relatively limited. Our enabling law . . . does not require assessment of comparative effectiveness and the legislative history made it very clear there was no relative effectiveness requirement."). Perhaps unintentionally, this duty is expanding with the advent of the recently enacted biosimilar approval pathway, described *supra* Part II.A.2.

65. See generally 21 C.F.R. § 316 (2012).

66. 21 C.F.R. § 316.3(13)(i) (2012) ("[A] drug composed of small molecules, a drug that contains the same active moiety as a previously approved drug and is intended for the same use . . . except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug.>").

and larger drugs (“macromolecules”),⁶⁷ a category which encompasses and delineates between protein drugs, polysaccharide drugs, polynucleotide drugs, and “[c]losely related, complex partly definable drugs with similar therapeutic intent.”⁶⁸

The FDA has created a thorough framework to compare the generic versions of small-molecule drugs with their pioneer counterparts. In making these determinations, the agency considers a variety of distinctions⁶⁹: namely, the drugs’ therapeutic equivalence, pharmaceutical equivalence, and bioequivalence. To be therapeutically equivalent, the two small-molecule drugs must be pharmaceutically equivalent and bioequivalent.⁷⁰ According to the FDA’s Orange Book,⁷¹ pharmaceutical equivalence means that two drugs have the same active ingredients, are of the same dosage form, use the same route of administration, and are identical in strength or concentration.⁷² Bioequivalence means the “equivalent release of the same drug substance from two or more drug formulations.”⁷³ Therapeutic equivalence means that two drugs are pharmaceutical equivalents that can be expected to have the same clinical effect and safety profile when prescribed according to specified conditions, and do not present any bioequivalence problems.⁷⁴

Presently, there is no Orange Book equivalent for biologics. For reasons described below, perhaps there should be, because biologics and their generic biosimilars pose unique challenges in evaluating similarity.

2. Separate Procedural Consequences for Small-Molecule Drugs and Biologics

Differences in defining drugs can lead to different procedural consequences, such as the means by which these drugs are approved for commerce.⁷⁵ In the case of small-molecule drugs, manufacturers must apply for a

67. *Id.* § 316.3(13)(ii) (“[A] drug composed of large molecules (macromolecules), a drug that contains the same principal molecular structural features (*but not necessarily all of the same structural features*) and is intended for the same use as a previously approved drug, except that, if the subsequent drug can be shown to be clinically superior, it will not be considered to be the same drug.” (emphasis added)).

68. *Id.* § 316.3(13)(ii)(A)–(D).

69. *See, e.g.*, *Solvay Pharm., Inc. v. Ethex Corp.*, No. Civ. 03-2836 JRTFLN, 2004 WL 742033 (D. Minn. Mar. 30, 2004).

70. *Id.* at *2 (“[These generic applications require] the manufacturer of the similar drug to demonstrate that the two drugs are therapeutically equivalent, that is pharmaceutically equivalent and bioequivalent.” (footnotes omitted)).

71. FOOD & DRUG ADMIN., APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (2012), available at <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071436.pdf> [hereinafter ORANGE BOOK].

72. *Id.* at vi–vii; *see also* 21 C.F.R. § 320.1(c) (2012).

73. 21 C.F.R. § 320.1(f) (2012); *id.* § 355(j)(8)(B); ORANGE BOOK, *supra* note 71, at viii.

74. ORANGE BOOK, *supra* note 71, at vii.

75. *See generally* 21 U.S.C. § 355 (2011).

New Drug Application (“NDA”) to bring their new product to market.⁷⁶ Under the Drug Price Competition and Patent Term Act (commonly referred to as the Hatch-Waxman Act), generic small-molecule drug manufacturers may take advantage of an accelerated approval pathway called an Abbreviated New Drug Application (“ANDA”), which references a previously approved drug. In order to make use of the accelerated pathway, the application must contain information showing that the active ingredients in the generic drug are the same⁷⁷ as those of the pioneer, that they share the same route of administration, dosage form, and strength,⁷⁸ and that the two drugs are bioequivalent.⁷⁹ This pathway allows generic sponsors to bring their product to market without the same kind of clinical showing required for the pioneer drug by relying on the latter’s clinical data, thereby accelerating the availability of lower-cost generics to patients.

In contrast to these procedures for small-molecule drugs, there are several avenues presently available for moving biologic drugs through the FDA’s regulatory process.⁸⁰ As a brief overview, the primary route for obtaining approval for biologic drugs is for manufacturers to pursue a new Biologic License Application (“BLA”), as set forth in the PHSa. A small number of biologic drugs can make use of the FDCA section 505(b)(2), the original pathway for small-molecule drug approval. For biosimilars, this latter approval pathway is only available to biosimilars referencing a limited number of biologics approved through new drug applications (“NDAs”).⁸¹

As for generic small-molecule drugs, the FDA may approve biosimilars via a different route than the one for their respective pioneer biologic drugs. The BPCIA, enacted as part of the Patient Affordable Care Act on March 23, 2010, creates a shortcut for biosimilar approval. It amends the PHSa section 351(k) to create an “abbreviated licensure pathway” for biological products shown to be biosimilar to a reference product already licensed by the FDA. Use of a pioneer’s clinical drug data to facilitate approval and gain the “biosimilar” label is intended to expedite the presence of these biosimilar drugs on the market.⁸²

According to the revised standards of section 351(k), a proposed biological product with demonstrated biosimilarity (i.e., a “biosimilar” product) can come to market by relying on certain existing scientific knowledge pertaining to the reference product.⁸³ The statute provides that biosimilars may

76. *Id.* § 355(j).

77. *Id.* § 355(j)(2)(A)(ii)(I–II).

78. *Id.* § 355(j)(2)(A)(iii).

79. *Id.* § 355(j)(2)(A)(iv).

80. Liang, *supra* note 7, at 384–92.

81. See Noel Courage & Ainslie Parsons, *The Comparability Conundrum: Biosimilars in the United States, Europe and Canada*, 66 FOOD & DRUG L.J. 203, 213 (2011).

82. This approach is similar to that created for generic small-molecule drugs in the Hatch-Waxman Act. See 21 U.S.C. § 355(j).

83. 42 U.S.C. § 262(k)(2)(A)(i)(I–V) (2011).

also be found “interchangeable” with a pioneer product, if the biological product is both biosimilar to and “expected to produce no meaningful clinical difference” from the reference product.⁸⁴ As others have noted, this distinction means that “interchangeable” is a higher bar than “biosimilar.”⁸⁵

3. A New Challenge: Defining the Highly Similar Biologic

Early in 2012, the FDA published a Draft Guidance describing how a biosimilar manufacturer might craft an application to navigate this abbreviated approval pathway.⁸⁶ According to the Draft Guidance, the FDA must find that a biosimilar is “highly similar” to the reference product, with “no clinically meaningful differences” between the biosimilar and the reference drug in terms of “safety, purity, and potency.”⁸⁷ To meet these requirements, a biosimilar must satisfy a sophisticated totality-of-the-evidence standard, including comparisons of the biosimilar and the reference drug with respect to structure, function, animal toxicity, pharmacochemical attributes such as pharmacokinetics and pharmacodynamics, clinical immunogenicity, and clinical safety and effectiveness.⁸⁸ The same concerns must be satisfied for “interchangeable” biologics, with the additional requirement of clinical similarity. This latter requirement is phrased so as to be open ended, however, as the amount of clinical data required will depend on “the extent of residual uncertainty about the biosimilarity of the two products.”⁸⁹

Ultimately, the FDA has the final decision on adequacy of scientific justification.⁹⁰ Consequentially, the FDA has the discretion to determine that any particular element—for example, the studies on biological similarity, effects on animals, and clinical studies of safety, purity, or potency—is unnecessary in a section 351(k) application.⁹¹ Further, “clinically meaningful” merely requires a difference in the *expected range* of safety, potency, and purity, not a *slight difference* in the rates of occurrence of adverse events when comparing two biological products.⁹² At present, it is unclear how the FDA will interpret “highly similar” in the context of biosimilar applications.

84. *Id.* § 262(k)(4).

85. Jonathan Stroud, *The Illusion of Interchangeability: The Benefits and Dangers of Guidance-Plus Rulemaking in the FDA’s Biosimilar Approval Process*, 63 ADMIN. L. REV. 599, 626 (2011).

86. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT (2012), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf> [hereinafter DRAFT GUIDANCE].

87. *Id.* at 3.

88. *Id.* at 7.

89. *Id.* at 12.

90. See generally *id.* at 5 (giving the FDA discretion to require less data from studies).

91. *Id.*

92. *Id.* at 8 (emphasis added).

Manufacturing concerns pose a special problem in creating this definition. Other scholars have discussed the difficulty of producing therapeutically equivalent biosimilars,⁹³ and one described the situation as follows: “Because of the differences in production and size between biologics and chemical drugs, as well as the unique cellular source of biologics, it is nearly impossible to make truly identical copies of a protein using two different production cell lines.”⁹⁴ This impossibility, he argues, ultimately precludes generation of a true generic biologic molecule. The subsequent therapeutic implications are likely to be profound, and others have noted that “[i]t is a particular challenge with biosimilars to know which variations matter clinically and which will have no impact.”⁹⁵ The FDA has also identified some additional problematic properties of biosimilars that cannot be quantified but nonetheless impact their function: specifically, post-translational modifications, three-dimensional folding, and aggregation,⁹⁶ which may be affected by manufacturing processes. The FDA offers guidance on quality controls,⁹⁷ and this will be presumably be useful for biosimilar development.

In sum, manufacturers face at least two foreseeable challenges with respect to the approval process: FDA development of its biosimilar approval mechanism and difficulties of manufacturing. These complications have not hindered generic pharmaceutical companies from anticipating the FDA’s interpretation and planning their biosimilar development accordingly.⁹⁸ For example, representatives of Sandoz Biopharmaceuticals—a leading generics manufacturer—describe “goal posts,” which define the desirable pharmacochemical attributes for a particular biosimilar.⁹⁹ These goal posts represent the range of characteristics of the “originator” pioneer molecule that occur through manufacturing change; i.e., due to scaling up the manufacturing process or transferring the manufacture to other facilities. If the

93. Specifically, sources have addressed biochemical and pharmacological similarities: structure / composition, pharmacokinetics, and efficacy in animals, as discussed in the DRAFT GUIDANCE, *supra* note 86; *see, e.g.*, Woodage, *supra* note 50, at ¶ 23 (“A possible avenue for gaining experience with the abbreviated-approval process is . . . start[ing] with ‘baby steps,’ initially considering less complex biologics, such as those molecules that can be produced in bacterial cells and have a lower risk of immunogenicity because they do not undergo post-translational glycosylation.”).

94. Liang, *supra* note 7, at 371.

95. Courage & Parsons, *supra* note 81, at 204.

96. Berkowitz et al., *supra* note 8, at 527.

97. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY Q11 DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES, 16 (2012), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf> (“Data derived from commercial-scale batches should confirm results obtained from small-scale studies used to generate data in support of process validation. . . . The limit of in vitro cell age for commercial production should be assessed.”).

98. Mark McCamish & Gillian Woollett, *Worldwide Experience with Biosimilar Development*, 3 MABS 209 (2011).

99. *Id.* at 214. The authors illustrate the concept nicely in Figure 4.

biosimilar's activity falls within the pioneer's benchmarks, the biosimilar manufacturer should feel confident that the FDA will accept their product.¹⁰⁰ Absent firmer guidance from the FDA regarding how to make a "highly similar" drug, this initial approach seems reasonable.

Although the FDA has not yet approved any biosimilars for the U.S. market, the TNF α inhibitors serve as a useful example of things to come, as biosimilar versions of Enbrel have already been developed and characterized in South Korea.¹⁰¹ Recent research upon the effects of these biosimilars has already illustrated some of the key concerns. Despite similar pharmacokinetic profiles, one study noted that more subjects receiving the biosimilar drug for treatment reported adverse side effects than did subjects who received Enbrel.¹⁰² In a subsequent comparative study of two Enbrel biosimilars, the authors identified multiple—but arguably minor—differences in the structure of one biosimilar as compared to that of Enbrel.¹⁰³ After performing a battery of functional assays, however, the researchers ultimately concluded that there was little observable functional difference between the two products, despite the lack of perfect structural similarity.¹⁰⁴

It is arguable whether these types of scientific findings, absent further clinical showing, would be sufficient to constitute the high similarity required to approve a biosimilar through the accelerated pathway. Approval would certainly seem to require the FDA to squint at the structural data. The FDA is not interested in perfect similarity between two biologic molecules, according to the Draft Guidance; rather, the FDA will focus upon the lack of meaningful clinical differences between Enbrel and any biosimilar attempting to replicate its therapeutic effects.

Thus, if the biosimilar's manufacturers were to pursue its approval for the U.S. market, the kinds of differences observed above may not torpedo its

100. *Id.* at 212 ("If the [biosimilar] product attributes fall within the variability of the originator molecule after manufacturing change, then the biosimilar should be considered 'highly similar.'").

101. Namyi Gu et al., *Comparative Pharmacokinetics and Tolerability of Branded Etanercept (25 mg) and Its Biosimilar (25 mg): A Randomized, Open-Label, Single-Dose, Two-Sequence, Crossover Study in Healthy Korean Male Volunteers*, 33 CLINICAL THERAPEUTICS 2029 (2011); Qingqiao Tan et al., *Characterization and Comparison of Two Commercially Available TNF Receptor 2-Fc Fusion Protein Products*, 4 MABS 761 (2012); SoJeong Yi et al., *Comparative Pharmacokinetics of HD203, a Biosimilar of Etanercept, with Marketed Etanercept (Enbrel®): A Double-Blind, Single-Dose, Crossover Study in Healthy Volunteers*, 26 BIODRUGS 177 (2012) (finding similar pharmacokinetic profiles when tested in healthy adults).

102. Gu, *supra* note 101. Eleven out of twenty-one subjects receiving biosimilar therapy reported adverse effects, whereas eight of twenty-one Enbrel-treated subjects did.

103. Tan, *supra* note 101 (recognizing a protein sequence difference of only two amino acids, relatively low sialylation of N-oligosaccharides, and differences in charge attributes between the two drugs).

104. *Id.* at 761 ("Interestingly, [the biosimilar] exhibited similar affinity and bioactivity levels compared with [Enbrel] despite the obvious difference in primary structure and partial physiochemical properties.").

approval through the accelerated pathway, particularly if the drug's safety profile is strong. On the other hand, doctors and their patients would benefit from a greater understanding of the biosimilar's ability to reduce or eliminate the symptoms of disease, such as joint degeneration or pain in RA patients, but these potential clinical outcomes cannot be properly extrapolated from these comparisons as performed.

B. *Making the Decisions: A Role for Experts*

As described above, the FDA's competency is evaluating drug safety and efficacy on the basis of data submitted in a premarket application. Approving biosimilars requires the FDA to answer a new question: whether a new biologic drug is similar enough to its pioneer that the latter's data can apply to the former, absent an actual showing to this effect. It is important to emphasize here the distinction that generic small-molecule drugs are "the same as" their pioneers, whereas biosimilars are "highly similar" to theirs. Accordingly, the question is qualitatively different, and the factors implicated in a "highly similar" analysis invite a more nuanced approach. The difficulties in biosimilar manufacture further complicate the picture, as discussed previously. Finally, the FDA's own Draft Guidance leaves much flexibility in terms of what data is sufficient to draw the "highly similar" or "interchangeable" comparisons. Overall, these complications render the biosimilar approval process significantly different from the approach to the generic small-molecule drug approval. Because these questions are new and different, the "highly similar" analysis raises significant institutional competency concerns.

It is possible that the FDA will be able to acquire the competency to address these concerns as it gains familiarity with biosimilar applications, in the same manner that it considers applications for generic versions of small-molecule drugs.¹⁰⁵ An alternate means of alleviating some of these concerns is for the FDA to seek outside expert help in interpreting the premarket similarity of these drugs by convening one of its thirty-three advisory committees.¹⁰⁶ The FDA regularly involves experts in the consideration of new drug applications. Following receipt and review of an application for a new drug or biologic, the FDA determines whether outstanding questions need to be addressed.¹⁰⁷ If so, the FDA then convenes advisory committee meetings for the purpose of soliciting expert input.¹⁰⁸ Observers have noted that the

105. See *supra* note 76 and accompanying text.

106. See *Advisory Committees*, FOOD & DRUG ADMIN., <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/default.htm> (last updated Dec. 16, 2011).

107. Jeffrey F. Smith et al., *FDA Advisory Meeting Outcomes*, 11 NATURE REVIEWS DRUG DISCOVERY 513, 513 (2012).

108. *Id.*

FDA's decision to approve a new drug often closely tracks the advice provided by the experts at these advisory meetings.¹⁰⁹

The FDA exercises its discretion in deciding whether to convene an advisory committee.¹¹⁰ Generally, the FDA may choose to do so when the matter is of significant public interest, controversial, or would benefit from a special type of expertise.¹¹¹ In the context of biosimilar drug approval, there will necessarily be an outstanding question of whether the drug is highly similar to its reference. Logically, the FDA should reach out to experts with strong expertise in structural and functional biology in order to reach the best answer. The FDA will likely be amenable to this suggestion, as they already sought input from stakeholders on multiple areas relevant to biosimilar development in the process of developing the Draft Guidance,¹¹² and they are thought to have a rather conservative approach to the approval of new drugs in general.¹¹³

Use of experts is no panacea. "Experts" are not fungible, and the FDA's selection criteria for committee membership are fairly open ended: members should be technically qualified experts in their field and have experience interpreting complex scientific data.¹¹⁴ Further, despite the selection of independent experts, the FDA allows representatives from the pharmaceutical industry to attend advisory committee meetings. Some authors have argued that the industry's influence makes the FDA susceptible to agency cap-

109. *Id.* at 514 ("The FDA approved 88% of the original NDAs or BLAs that were endorsed by its advisory committees, and did not approve 86% of those that the committees did not endorse.").

110. FOOD & DRUG ADMIN., GUIDANCE FOR THE PUBLIC AND FDA STAFF ON CONVENING ADVISORY COMMITTEE MEETINGS: DRAFT GUIDANCE (2008), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125651.pdf>.

111. *Id.* at 4.

112. *Id.* As reflected in the Draft Guidance, these include: (1) factors that the FDA should consider in evaluating "highly similar;" (2) factors that the FDA should consider in determining what analytical, animal, or clinical studies should be used to assess the potential impact of structural differences; (3) the range of structural differences consistent with "highly similar;" (4) circumstances where the FDA should find that additional animal or clinical studies are unnecessary.

113. See Nicholas S. Downing et al., *Regulatory Review of Novel Therapeutics—Comparison of Three Regulatory Agencies*, 366 NEW ENG. J. MED. 2284, 2288 (2012). At least, so argue these authors, based on a finding that the FDA only approved 61.8% of new drugs after one cycle of review, which classified it as conservative compared with other international drug approval agencies.

114. In selecting experts for committee participation, a key concern is whether there is a conflict of interest. See U.S. FOOD & DRUG ADMIN., GUIDANCE FOR THE PUBLIC, FDA ADVISORY COMMITTEE MEMBERS, AND FDA STAFF ON PROCEDURES FOR DETERMINING CONFLICT OF INTEREST AND ELIGIBILITY FOR PARTICIPATION IN FDA ADVISORY COMMITTEES (2008), available at <http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM125646.pdf>. Otherwise, membership requirements are minimal, at least as stated by the FDA; *Advisory Committees: Membership Types*, FOOD & DRUG ADMIN., <http://www.fda.gov/AdvisoryCommittees/AboutAdvisoryCommittees/CommitteeMembership/MembershipTypes/default.htm> (last updated July 15, 2010).

ture.¹¹⁵ Other safeguards are needed to alleviate these concerns, and one possibility is increased monitoring of postmarket safety data for biosimilars.

C. Making the Decisions: A Role for Postmarket Safety Data

Approving any drug is a health and safety gamble, even when extensive preclinical testing occurs. Although much previous scholarship has focused upon challenges in biosimilar approval, an equally concerning issue is how best to make certain that the approval, once earned, was in fact merited.

If a drug is shown to be unsafe, there are procedures in place to identify and remove approved drugs from the market. Once a drug is on the market, CDER handles reports related to drug safety, and individuals have the opportunity to submit accounts of drug-related health incidents. But it is the manufacturers and not the FDA that have the burden of following up on safety concerns for a particular drug.¹¹⁶ Although the FDA can require drug manufacturers to submit reports of adverse events or manufacturing problems,¹¹⁷ this system is rife with administrability problems, as others have amply documented.¹¹⁸

Generally, if a drug poses health risks, comparative effectiveness data could suggest alternatives to its use. Since the FDA does not track this information, however, it may never be gathered.¹¹⁹ If these data *are* to be collected, a reasonable argument can be made that this burden should not fall upon the drug manufacturers. The perception of a conflict of interest may be too difficult to eliminate, even in well-conducted studies. For example, recent work suggests that physicians are less likely to view research funded by a pharmaceutical company as conducted with a high level of rigor and may be consequently more reluctant to prescribe these drugs.¹²⁰ Even if pharma's

115. See, e.g., Amalea Smirniotopoulos, *Bad Medicine: Prescription Drugs, Preemption, and the Potential for a No-Fault Fix*, 35 N.Y.U. REV. L. & SOC. CHANGE 793, 808–12 (2011) (defining agency capture as “[m]anufacturers’ influence over regulators and malfeasance”).

116. 21 U.S.C. § 355(k)(3) (2011).

117. See *Postmarketing Surveillance Programs*, FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm090385.htm> (last updated Aug. 19, 2009).

118. See, e.g., Matthew Gordon, *Improving Post-Approval Risk Surveillance for Drugs: Active Post-Market Risk Identification*, 15 MICH. TELECOMM. & TECH. L. REV. 297 (2008), available at <http://www.mttl.org/volfifteen/gordon.pdf>; Smirniotopoulos, *supra* note 115, at 809 (“[P]atients with serious or terminal illnesses and their families have long criticized the FDA for failing to approve new drug therapies fast enough, or for revoking approval after a drug proves to be unsafe for some patients.”).

119. E.g., Furst et al., *supra* note 35, at 348 (“Once a drug is approved for a particular indication, manufacturers have no incentive to conduct expensive head-to-head trials to determine the relative benefit of the new treatment against the current best treatment.”).

120. Aaron S. Kesselheim et al., *A Randomized Study of How Physicians Interpret Research Funding Disclosures*, 376 NEW ENG. J. MED. 1119 (2012).

studies reveal important results, the effect of this perception may obfuscate the true value of the findings.¹²¹

The present systems indicate significant problems with collecting these data. However, they should be collected if consumers are to be protected adequately. Although bioequivalence for a drug is determined prior to its market availability, much safety-related information only becomes available after the drug reaches consumers, and clinical trial information only serves as a proxy for subsequent treatment protocols.¹²² Because these data more accurately indicate the performance of the drug in the relevant population, consideration of this postmarket safety data (also termed pharmacovigilance) should be at least as important to analyses of drug safety as is premarket safety data.

In particular, postmarket safety data can be used to distinguish among similar drugs. To anticipate how the FDA will handle future assessments of drug similarity, the FDA's treatment of a family of similar selective small-molecule inhibitors of cyclooxygenase-2 (COX2) may be informative. These drugs, Celebrex (celecoxib), Bextra (valdecoxib), and Vioxx (rofecoxib), were originally approved to treat pain via inhibition of COX2 activity,¹²³ and although these three drugs do not have perfectly identical structures, they do share similar functions. They thus may be considered MTDs.¹²⁴ The FDA subsequently revoked Vioxx's approval following significant elevated rates of heart attacks in patients, to great publicity, and Bextra's manufacturer later voluntarily pulled it from the market.¹²⁵ Only Celebrex remains on the U.S. market,¹²⁶ despite an increased incidence of similar cardiovascular events as shown for the other two drugs.¹²⁷

This story highlights certain clear benefits of postmarket safety data, as they reveal the details of a drug's real world performance. Further, this example illustrates the special challenge facing the FDA if safety problems

121. *Id.* at 1125 ("Pharmaceutical companies seeking to enhance the appropriate use of important new products or to expand the appropriate uses of existing products must address the attitudes that our survey revealed, so that the credibility of the results of industry-supported trials is more likely to be based on methodologic rigor than on funding sources.").

122. *See, e.g.,* Iannone et al., *supra* note 29, at 1179 ("Our study provides further evidence that the real-life treatment of patients with RA may be different from that of randomized clinical trials.").

123. *See COX-2 Selective (Includes Bextra, Celebrex, and Vioxx) and Non-Selective Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*, FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/drugsafety/postmarketdrugssafetyinformationforpatientsandproviders/ucm103420.htm> (last updated Nov. 27, 2012) [hereinafter *NSAIDs*].

124. Sid M. Wolfe, WORST PILLS, BEST PILLS: A CONSUMER'S GUIDE TO PREVENTING DRUG-INDUCED DEATH 303 (2005) ("Valdecoxib is another redundant "me-too" drug in the crowded NSAID family of drugs. This drug is chemically similar to celecoxib . . .").

125. *NSAIDs*, *supra* note 123.

126. *Id.* In contrast, all three drugs were pulled from Canada's market.

127. Scott D. Solomon et al., *Cardiovascular Risk Associated with Celecoxib in a Clinical Trial for Colorectal Adenoma Prevention*, 352 NEW ENG. J. MED. 1071 (2005).

emerge for drugs with a high degree of structural resemblance. It will not always be evident whether the adverse events stem from the parts of the drugs that make them structurally similar, so that all should be pulled from the market, or from those that are different between the members of the drug family, which would justify keeping others available for patients' use. Problems will arise no matter which response the FDA makes. One possibility is to pull all members of the drug family from the market, but this may be an overreaction, particularly when some patients depend greatly upon them. The alternative is for the FDA to consider each drug separately, requiring a great deal of time and expense. But, as the COX2 inhibitor example shows, mere structural and functional similarity of drugs does not guarantee that the FDA will respond to their identified risks in the same manner.

Postmarket safety data also confers other, more politic, advantages over premarket safety data. Even if the FDA chooses to compel the industry to conduct clinical trials, it must still rely heavily upon the industry's own representations of fact in order to bring drugs to market. A stronger focus on postmarket safety data obviates these concerns and provides a deeper and more accurate picture of the drug's performance in the entire population than even premarket Phase III clinical trials can provide. Of interest, recent evidence suggests possible misrepresentation of Celebrex's safety data in persuading the FDA to allow Pfizer to keep it on the market.¹²⁸ Whether or not this allegation is ultimately borne out, this saga serves as a cautionary tale, highlighting the weakness of the FDA as an independent evaluator of drug safety.

While the COX2 inhibitors are small-molecule drugs and not biologics, their story underscores some important concerns that the FDA will face in handling the approval of biologic drugs that are not only similar, but highly similar. As patents for many pioneer drugs are expected to expire soon, the importance of carefully tracking safety data for approved biosimilars will become increasingly apparent. Though the FDA's present concern is how much premarket safety data should be required for biosimilar approval, it should also invest heavily in closely tracking the postmarket performance of these drugs.

III. INTERPRETING BIOLOGICAL SIMILARITY: PATENT LAW AS DECISION MAKER

Like the FDA, the patent legal system must also routinely interpret biological similarity. This system, generally comprising the USPTO and the Federal Circuit, answers statutory questions of biologic drug patentability or

128. See Katie Thomas, *In Documents on Pain Drug, Signs of Doubt and Deception*, N.Y. TIMES (June 24, 2012), http://www.nytimes.com/2012/06/25/health/in-documents-on-pain-drug-celebrex-signs-of-doubt-and-deception.html?pagewanted=all&_r=0 (“[The FDA] swallowed [Pfizer’s] story, hook, line, and sinker.”).

of infringement. In patent law, biochemistry and pharmacology are part of the so-called unpredictable arts,¹²⁹ as small alterations in small-molecule and biologic drugs can affect efficacy and function in surprising ways.¹³⁰ Nevertheless, it is equally clear that not all small changes merit a patent.

The context of interpretation is different from that of the FDA: the patent legal system only decides whether the drug merits patent protection and ignores questions of safety and efficacy. But because both institutions evaluate biological similarity, it is worth exploring differences in their definitions and the extent to which the patent legal system adopts the FDA's terminology.

A. Hurdles to Biologic Patentability

Patentability is evaluated in the course of a biologic's application to the USPTO or in the course of a patent infringement suit. Obtaining patent protection requires a drug to clear a variety of patentability hurdles. The essence of the patent system is to reward inventions that are new, useful, and nonobvious¹³¹ by affording the patent holder a significant property right: the ability to exclude others from making, using, and selling the invention.¹³² The invention itself is defined by a combination of the patent application's written description,¹³³ which must be enabling,¹³⁴ as well as the claims,¹³⁵ which precisely define the bounds of the invention. Although the subject matter of pharmaceutical drugs is necessarily complex, the Federal Circuit has stated that there is no particular "super-enablement" standard for biological or chemical patents.¹³⁶

129. See, e.g., *In re Fisher*, 427 F.2d 833, 839 (C.C.P.A. 1970) ("In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.").

130. The converse is also true: even though a disease may have obvious targets against which to develop a therapeutic, drugs typically have a very high failure rate in both preclinical and clinical trials.

131. See 35 U.S.C. §§ 101–103 (2011).

132. *Id.* § 154(a)(1) (2011).

133. See *id.* § 112; see also Sheila R. Arriola, *Biotechnology Patents After Festo: Rethinking the Heightened Enablement and Written Description Requirements*, 11 FED. CIR. B.J. 919, 936 (2002) ("For unpredictable arts [the written description] 'requires a precise definition, such as by structure, formula, chemical name, or physical properties.'" (citing *Fiers v. Revel*, 984 F.2d 1164, 1171 (Fed. Cir. 1993))).

134. See *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010). The written description must be sufficient to enable a person having ordinary skill in the art to make and use the invention without undue experimentation.

135. Arriola, *supra* note 133, at 919 ("The claims of a patent are prescribed by statute for the purpose of making the patentee define precisely the scope of the invention.").

136. See *Ariad*, 598 F.3d at 1352 ("The [written description requirement] never created a heightened requirement to provide a nucleotide-by-nucleotide recitation of the entire genus of claimed genetic material; it has always expressly permitted the disclosure of structural features common to the members of the genus.").

Further, a new biologic drug must be neither anticipated by¹³⁷ nor obvious in light of¹³⁸ the prior art in order for its inventor to obtain a patent thereon. These separate analyses have different foci and accordingly different implications for biologic drug patentability. Novelty is evaluated through a point-by-point comparison with another product or prior art reference.¹³⁹ By contrast, obviousness analyses depend upon the state of knowledge in the pharmaceutical and biomedical research fields at the time of drug development and the motivations to create particular therapeutics.¹⁴⁰

Patent infringement occurs when one group's product infringes a senior party's patent property right by making, using, selling, or importing the drug. The court may consider two questions, depending on which defenses the accused infringer asserts: (1) the manufacturer's patent validity,¹⁴¹ and if declared valid, (2) whether the alleged infringer's product infringes, either literally or under the doctrine of equivalents.¹⁴²

Beyond expensive patent infringement litigation costs, resolving these cases is likely to lead to significant administrative costs on future courts, which must evaluate extremely technical material in order to solve legal questions. Although many aspects of patentability are reviewed *de novo* on appeal and issues such as claim construction in one case may be non-precedential in another,¹⁴³ judges may still follow or rely on reasoning in a

137. 35 U.S.C. § 102 (2011), *amended by* Patent Law Treaties Implementation Act of 2012, Pub. L. No. 112-211, 126 Stat. 1527 (effective Dec. 18, 2013). Lack of novelty can only be established by a single prior art reference that discloses each and every element of the claimed invention, a fairly strict identity requirement for all elements of the claimed invention.

138. *Id.* § 103; Michelle L. Evans, *Establishing Obviousness of Biotechnology Patent Under 35 U.S.C.A. § 103*, 122 AM. JUR. 3D PROOF OF FACTS § 1 (2011) (“With chemical structures and sequence listings used in biotechnological patents, obviousness typically depends on the structural similarities and differences between the products claimed and the prior art. If a scientist of ordinary skill in the appropriate art would have been motivated to select and then modify a prior art compound to arrive at the compound claimed in the patent at issue with a reasonable expectation that the new compound would have similar or improved properties to the prior art compound, then obviousness is established.” (footnotes omitted)).

139. *See, e.g.*, *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005) (“[W]hen considering a prior art method, the anticipation doctrine examines the natural and inherent results in that method without regard to the full recognition of those benefits or characteristics within the art field at the time of the prior art disclosure.”).

140. *See* *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1965) (requiring comparison of the claimed invention with the pertinent prior art, from the perspective of an objective person having ordinary skill in the art); *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007) (finding that the PTO's exclusive use of the “teaching, suggestion, or motivation” test to determine obviousness is impermissible). Although rigid application of the TSM test is precluded by *KSR*, the doctrine is still frequently used in analyzing obviousness.

141. That is, whether the patent was improperly granted.

142. *See* *Graver Tank v. Linde Mfg. Co.*, 339 U.S. 605, 607–09 (1950); *see also infra* Part III.C.

143. *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1322 (Fed. Cir. 1999) (finding reliance on prior Federal Circuit case only allowed for issue preclusion and not precedential for the claim construction itself). Other lower courts may not feel the same way as the Federal

case that has similar legal issues but different scientific issues. These conceptual difficulties have the potential to create inconsistent or problematic precedent, if reasoning is improperly extrapolated between cases. Thus, careful attention must be paid to what similarity actually entails. Part III.B below discusses the reasoning in some recent cases pertaining to aspects of biological similarity, paying particular attention to the legal concepts of obviousness and equivalence.

B. *Defining Biologic Obviousness*

Obviousness is a statutory barrier to a drug's patentability.¹⁴⁴ While small-molecule drugs have long been subjected to analyses of obviousness, it is not clear that courts should extend the rationale in these earlier cases to questions of obviousness for biologic patentability, for reasons discussed below.

The common law test for obviousness has changed noticeably over time and can incorporate several levels of analysis. Earlier courts routinely applied the factors of the *Graham* test, which required an evaluation of the scope and content of the prior art, the relative skill of persons having ordinary skill in the pertinent art ("PHOSITAs"), and a subsequent point-by-point comparison between the new invention and the prior art to determine whether the invention was obvious.¹⁴⁵ Presently, the USPTO also considers whether there is a "teaching, suggestion, or motivation" to develop a drug that may render it obvious, but this test is not mandatory,¹⁴⁶ and the USPTO must take an expansive and flexible approach to evaluating obviousness.¹⁴⁷

The discussion must begin, as before, by distinguishing between small-molecule drugs and biologics. Small-molecule drugs are synthesized compounds with no natural role in biological function. Thus, it is extraordinarily difficult to look at a small-molecule drug and accurately predict its effects in the human body. Consequentially, new small-molecule drugs may easily dodge the obviousness bar. This ability seems less certain for biologics. Biologics, like small-molecule drugs, are fundamentally clusters of atoms. But unlike small-molecule drugs, they mimic molecules with highly specific, tightly regulated functions that have evolved over millennia.

Further, as discussed in the Introduction, "biologics" is itself a complicated term and these drugs pose concerns that small-molecule drugs avoid.

Circuit, however. *See, e.g.*, *Permacel Kansas City, Inc. v. Soundwich, Inc.*, No. 03-0766-CV-W-HFS, 2006 WL 1449979, at *3 (W.D. Mo. May 24, 2006) ("It would, however, be reckless, to say the least, for me to rule in a manner inconsistent with an unpublished opinion of a panel of the reviewing court.").

144. 36 U.S.C. § 103 (2011).

145. *Graham*, 383 U.S. at 17 (creating a four-factor test for obviousness).

146. *See KSR*, 550 U.S. at 399.

147. *Id.* at 415 (referencing the Court's long use of an "expansive and flexible" approach when considering questions of obviousness).

For example, biosimilars and bio-betters are designed to be structurally similar or highly similar to the reference, but may be functionally different due to manufacturing issues. Similar-impact biologics, which may have somewhat or very different structures, may be designed to have a similar function, as in the case of the TNF α inhibitors.

Rebecca Eisenberg has noted that courts have treated obviousness inquiries inconsistently, with alternating focus on the drugs' structure or on their function,¹⁴⁸ but suggests that were the Supreme Court to come down on one side or another, the Court would prefer the latter's more flexible approach.¹⁴⁹ But there is a logical disconnect in measuring the "obviousness" of an "unpredictable" compound before much is known about its function and effect.

The structural comparison part of the traditional obviousness analysis is straightforward and thus relatively unobjectionable. Obviousness of a drug is technically measured from the time of its invention (but from the filing date for patents filed after March 16, 2013).¹⁵⁰ This timing may be appropriate for analyses that compare drugs' atomic structures with those of prior art drugs, where differences in the drugs' blueprints are clear, discrete, and reliably identifiable. This point-by-point comparison of structural features provides a foundation by which a patent examiner can state whether the drug is obvious in light of the prior art.

The functional comparison part of this analysis is trickier, and warrants consideration of a long-established tradition of case law evaluating obviousness of the function of small-molecule drugs. In determining whether these drugs are obvious, courts will often evaluate so-called "secondary considerations" of obviousness, which include a showing of unexpectedly better results for a drug than would have been predicted by an objective PHOSITA of drug development. For example, courts have found that a new drug may not be obvious if the manufacturer can show that his product has greater utility than would normally be expected.¹⁵¹

Even so, superior properties of a subsequent small-molecule drug may not always be sufficient to render it nonobvious.¹⁵² Courts are willing to draw lines, but it is unclear where these lines should be drawn. For example,

148. See Rebecca S. Eisenberg, *Pharma's Nonobvious Problem*, 12 LEWIS & CLARK L. REV. 375, 407 (2008).

149. *Id.*

150. Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 3(c), 125 Stat. 284 (2011).

151. *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) ("Given a presumption of similar properties for similar compositions, substantially improved properties are ipso facto unexpected."); *In re Blondel*, 499 F.2d 1311, 1315 (C.C.P.A. 1974) ("[Chemical compounds are nevertheless unobvious and patentable if their proofs show . . . that the increase in duration of activity is greater than those skilled in the art would have any reason to expect.>").

152. See, e.g., *Aventis Pharma Deutschland v. Lupin, Ltd.*, 499 F.3d 1293 (Fed. Cir. 2007) (finding obvious the superior performance of a drug composed of stereoisomers with

courts have shown some disagreement over whether the results themselves should be unexpected or whether the magnitude or degree of the results should be unexpected.¹⁵³ Even observed synergy, a kind of unexpectedly superior result, may not save a combination drug from invalidation for obviousness if the motivation to create the drug was obvious.¹⁵⁴ While the logic of these cases is informative, they concern the properties of small-molecule drugs. It is not clear how far their rationale will, or should, logically extend to cases involving biologics.

Arguably, the obviousness analysis should be different when considering development of biologics than for small-molecule drug therapies. In the course of drug development, manufacturers are guided by the desire to develop effective therapies for a particular disease. A PHOSITA will assuredly appreciate the logical incentives for developing a particular biologic drug; indeed, failure to do so would lead to much wasted time and effort by the developer. Often, the reasonable starting place is the underlying molecular mechanism of a disease, such as the pathologically elevated levels of TNF α that characterize RA. For example, if a PHOSITA wants to block TNF α from binding a receptor, he can effectively trick TNF α into binding a decoy target designed to mimic the receptor. Enbrel is a prime example of this type of drug. In these cases, the target is obvious. The biochemical methods and protocols are familiar and well characterized. The prior art is often the components of the body itself, shaped by millennia of human evolution. Importantly, there is a reasonable expectation that the drug will work for the intended purpose.¹⁵⁵ But this raises the question of whether all biologic drugs should be considered inherently obvious, and therefore unpatentable, simply because there are strong incentives to pursue them.

heightened bioactivity, when the improved bioactivity was expected due to an increase in the amount of the effective stereoisomer).

153. See *In re Merck*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (“Regarding the anticholinergic effect, . . . both drugs have anticholinergic effects but to a different degree. These are not truly unexpected results. . . . The core of it is that, while there are some differences in degree between the properties of amitriptyline and imipramine, the compounds expectedly have the same type of biological activity.”).

154. See *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997) (“Evidence of secondary considerations, including evidence of unexpected results and commercial success, are but a part of the ‘totality of the evidence’ that is used to reach the ultimate conclusion of obviousness.”). In *Richardson-Vicks*, another small-molecule drug case, the Federal Circuit affirmed a finding of obviousness even when “synergy” was observed in a novel drug combination, following the district court’s rejection of an examiner’s finding of nonobviousness due to unexpectedly superior analgesic properties (merely additive effects would have protected 50% of subjects, but the drug protected 80%). The district court reasoned that the motivation to combine the two pain medications would have been obvious.

155. See *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009).

Presently, biologic drugs with the same target, similar structure, and virtually identical function can obtain patents.¹⁵⁶ Methods of creating biologic drugs may not be invalid for obviousness even if virtually identical drugs are created via the same mechanisms.¹⁵⁷ In some cases, abuse of the “unpredictable” label may render the obviousness analysis absurd.

In *Amgen*, the Federal Circuit considered two essentially indistinguishable means of producing biologically active erythropoietin (“EPO”),¹⁵⁸ an important regulator of blood production in the body which may be manufactured as a biologic drug. The Federal Circuit interpreted Roche’s patent claims as follows:

The cells described [in Roche’s patent] are “capable of glycosylating” EPO and are transfected with DNA encoding a polypeptide “having an amino acid sequence sufficiently duplicative of that of erythropoietin to allow possession” of the stated biological activities. Neither of these limitations . . . however, requires that the cells actually produce isolatable amounts of glycosylated EPO having the stated *in vivo* bioactivity.¹⁵⁹

The court distinguished these claims from those in Amgen’s patents, noting that “[i]n contrast, the asserted claims of [Amgen’s patents] *do* require actual production of isolatable amounts of the *in vivo* biologically active EPO glycoprotein.”¹⁶⁰ The court subsequently determined that Amgen’s claims were not invalid for obviousness, focusing upon what it saw as the “main difference” between the two patents: “the *actual production* of isolatable glycosylated EPO having the stated *in vivo* biological activities.”¹⁶¹ Notably, the court’s holding does not dwell on any rationale that Roche’s scientists might have had for originally selecting the cells that it chose to produce the EPO. Rather, the court dealt with the observation that Roche’s cells do, in fact, produce the desired glycosylated (biologically active) EPO by reasoning that “having the stated biological activity is one of hindsight, not of reasonable expectation of success at the time of the invention.”¹⁶²

156. As described in the discussion of TNF α inhibitor litigation, *supra* Part II.B, both antibodies were able to obtain patents.

157. See, e.g., *Amgen Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340 (Fed. Cir. 2009).

158. *Id.* at 1361 (“[Roche’s patent] recites a CHO cell—a mammalian cell capable of glycosylating EPO—transfected with a DNA sequence encoding a polypeptide having an amino acid sequence sufficiently duplicative of that of EPO to allow possession of the stated biological properties. Claims [in Amgen’s patents] recite processes of producing EPO that involve (a) growing mammalian cells transfected with DNA encoding EPO and (b) isolating from those cells glycosylated EPO having the stated biological properties.”).

159. *Id.* at 1361.

160. *Id.*

161. *Id.* (emphasis added).

162. *Id.* at 1363.

Even considering the unpredictability of the biochemical arts, this distinction may seem strange. Surely a PHOSITA, having set up a system specially designed to produce a biologic drug, would expect it to work for this purpose, even if actual production of biologics is a difficult and problematic endeavor. The reasoning in this case suggests that the obviousness hurdle can be an extraordinarily low bar to patentability, and much may depend on the claim drafter's skill.

At the most extreme end, some scholars have argued that the nonobviousness requirement should be eliminated altogether, as it generally creates perverse incentives in drug development, particularly because the drugs most likely to be effective would be especially vulnerable to this means of invalidation.¹⁶³ Given that the requirement does not seem to be much of a bar, perhaps it would not be missed too much. On the other hand, one possible argument for retaining the obviousness analysis in biologics cases is that it might be useful for some manufacturers to demonstrate unexpectedly superior properties in a given drug's structure. This argument resurrects some of the logic in small-molecule drug obviousness analyses, but perhaps there is still a place for this rationale.

The nonobviousness requirement raises a higher bar for biosimilars. The very nature of a highly similar product, for which similarity is an essential element of its design, seems to forbid its patentability altogether. As discussed previously, biosimilars are necessarily different from their reference drugs in ways that do not apply to generic small-molecule drugs due to their simpler means of manufacture, and the TNF α biosimilars in Part I show that structural and functional differences are entirely plausible. Accordingly, it is possible to conceive of biosimilars that could merit their own patent. Further, discussions of biosimilar patents do not preclude the issue,¹⁶⁴ although patent protection for biosimilars might be an undesirable strategy for other reasons.¹⁶⁵ Of course, introduction of unpatented biosimilars following expiry of the reference drug patent will avoid the problems of infringement and obviousness altogether.

163. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 536 (2009) ("It denies patent protection to the drugs that appear most likely to succeed at the time they are invented and that have expected beneficial properties, i.e., the drugs that appear most promising in early research."). Roin goes on to say: "The courts and PTO apply this test without hesitation, finding drugs to be unpatentable whenever their therapeutic properties are considered unsurprising." *Id.* However, his claim appears largely to revolve around alterations to typical small-molecule drugs.

164. See Yaniv Heled, *Parents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419 (2012), available at <http://www.mtlr.org/voleighteen/heled.pdf>; D. Alan White, Comment, *The Doctrine of Equivalents: Fairness and Uncertainty in an Era of Biologic Pharmaceuticals*, 60 EMORY L.J. 751, 762 (2011).

165. See generally Heled, *supra* note 164. Heled essentially argues that the statutory exclusivity period created by the BPCIA for biosimilar drugs precludes the need to obtain a patent therefor.

C. Defining Biologic Equivalence

The doctrine of equivalents is a weapon in a patentee's arsenal to exclude competition by an extremely similar product. The thrust of the doctrine of equivalents is that a product or process that does not literally infringe upon the express terms of a patent claim "may nonetheless be found to infringe if there is 'equivalence' between the elements of the accused product or process and the claimed elements of the patented invention."¹⁶⁶ Thus, in order to find infringement under the doctrine of equivalents, a court must determine that the potentially infringing product infringes each element of the patented product.¹⁶⁷ The two traditional tests of equivalence are (1) to compare differences between products to determine if these changes are "insubstantial," and (2) to determine if the accused product's element "performs substantially the same function in substantially the same way to obtain the same result" as the claim limitation,¹⁶⁸ an analysis known as the function-means-result test. A determination of product equivalence is, intuitively, a complicated task that requires significant factual inquiry¹⁶⁹ and is reviewed under the clear error standard.¹⁷⁰

A similarly flexible rationale is applied when determining equivalence of competitive products.¹⁷¹ In the case of drugs, courts consider both a com-

166. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 21 (1997) (citing Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605 (1950)); see also Lupin Ltd. v. Abbott Labs., 491 F. Supp. 2d 563, 568 (E.D. Va. 2007) (citing Zelinski v. Brunswick Corp., 185 F.3d 1311, 1316 (Fed. Cir. 1999)), *aff'd sub nom.* Abbott Labs. v. Sandoz, Inc., 566 F.3d 1282 (Fed. Cir. 2009).

167. Paul N. Katz, *The Doctrine of Equivalents and Its Impact on "Designing Around,"* 4 FED. CIR. B.J. 315, 324 (1994) ("To aid the federal district courts in determining what is 'substantially the same,' the Federal Circuit endorsed the 'All Elements' rule which states that equivalents cannot exist per se unless a literal or equivalent counterpart exists in the accused device for each and every recited claim element.").

168. Warner-Jenkinson, 520 U.S. at 38 (quoting Union Paper-Bag Mach. Co. v. Murphy, 97 U.S. 120, 125 (1878)); see also *id.* at 19 ("In the Court's view, the particular linguistic framework used to determine 'equivalence,' whether the so-called 'triple identity' test or the 'insubstantial differences' test, is less important than whether the test is probative of the essential inquiry: Does the accused product or process contain elements identical or equivalent to each claimed element of the patented invention?").

169. Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 609 (1950) ("What constitutes equivalency must be determined against the context of the patent, the prior art, and the particular circumstances of the case.").

170. Abraxis Biosci., Inc. v. Mayne Pharma (USA) Inc., 467 F.3d 1370, 1379 (Fed. Cir. 2006) ("Unlike claim construction, a matter of law reviewed de novo, infringement under the doctrine of equivalents is a factual determination that we review for clear error.").

171. Graver Tank, 339 U.S. at 609 ("Equivalence, in the patent law, is not the prisoner of a formula and is not an absolute to be considered in a vacuum. It does not require complete identity for every purpose and in every respect. In determining equivalents, things equal to the same thing may not be equal to each other and, by the same token, things for most purposes different may sometimes be equivalents.").

pound's structure and its function, and these comparisons may be qualitative or quantitative in nature.¹⁷²

While biochemistry is often thought of as an unpredictable art for which small changes can lead to significant and unexpected effects, some qualitative effects of changes are foreseeable.¹⁷³ This foreseeability applies to biologics in a way that it may not for entirely artificial small-molecule drugs. Proteins are composed of amino acids, which are discrete building blocks. In evaluating the equivalence of any parts of the protein, the primary focus must be on a protein's amino acid sequence—and not on any underlying DNA nucleotide sequence—because amino acids, not nucleotides, contribute directly to biologic function. As building blocks, amino acids are not fungible.¹⁷⁴ Accordingly, a change from one neutral amino acid to another may have no discernible effect on the protein's function,¹⁷⁵ but a change from a neutral amino acid to a charged amino acid may have significant functional consequences.¹⁷⁶ A final step is to consider the context of the placement of the mutation in the molecule.¹⁷⁷ All these qualitative aspects of protein composition can affect function and should factor into equivalence assessments.

It may be conceptually easier for courts to evaluate quantitative concerns in their equivalence inquiries, as suggested by the analyses of secondary considerations of obviousness, in Part III.B. As a recent example, the *Teva Biopharmaceuticals* district court considered whether a competitor therapeutic differed substantially from a biologic multiple sclerosis drug,

172. *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963) (“From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared.”).

173. *Graver Tank*, 339 U.S. at 609 (“Consideration must be given to the purpose for which an ingredient is used in a patent, the qualities it has when combined with the other ingredients, and the function which it is intended to perform. An important factor is whether persons reasonably skilled in the art would have known of the interchangeability of an ingredient not contained in the patent with one that was.”).

174. Arriola, *supra* note 133, at 927 (“Each of the twenty amino acids has distinct chemical properties: acidic, basic, uncharged polar, and nonpolar.”).

175. *Id.* (“A ‘conservative substitution’ refers to the swapping of amino acids within the same chemical property category, for example, switching one nonpolar amino acid for another. This type of modification, especially where it occurs away from a functional domain of the protein, may have little or no effect on the resulting biological function.” (footnotes omitted)).

176. Consider the wide variety of diseases that are linked to a single amino acid substitution as a result of a few nucleotides’ difference: sickle cell disease, bipolar disorder, macular degeneration, and some variants of Tay-Sachs disease. In these diseases, the pathology and symptoms directly stem from the change to the protein itself, and only indirectly from changes to the gene.

177. Some alterations may occur within a protein-binding or domain-mediating intermolecular recognition, where a change is likely to hugely affect function, whereas some may fall within a hydrophobic core or linker and have little effect.

based upon the numerical ratio of its amino acid composition.¹⁷⁸ In alleging infringement, the manufacturer showed that a deviation of up to 12% in the 6:2:5:1 ratio of four amino acids would not be expected to have a material effect on the biological activity of the drug.¹⁷⁹ Because the court found that the alleged infringer's drug differed in composition from the former drug only by 4.5%, the court determined that it would not be expected to have materially different biological activity.¹⁸⁰ When considering the functional significance of individual amino acids with respect to their placement in the protein, consideration of only numerical ratios may often be an insufficient metric in determining equivalence, for reasons described above.

Some scholars have suggested, via empirical studies, that use of the doctrine of equivalents is in decline.¹⁸¹ Yet it has been invoked in several recent cases as a means of finding infringement between biologic drugs.¹⁸² These cases illustrate the difficulties facing the courts in balancing similarities of these molecules with the unpredictability of the art itself. If the doctrine of equivalents is in decline, the advent of biosimilars may serve as an opportunity to resurrect it.¹⁸³

D. Expanding the Role of Regulatory Guidance

Answering questions of biologic similarity in the context of patent law reveals an abundance of moving parts. The complexity of these concerns raises significant questions about who should make decisions regarding biologic similarity. The statutory criteria constitute either questions of law, such

178. *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295 (S.D.N.Y. 2012).

179. *Id.* at 345.

180. *Id.* (“Accordingly, the molar ratio of [the infringer’s] proposed product is *insubstantially different* from approximately ‘6:2:5:1.’”) (emphasis added).

181. See, e.g., John R. Allison & Mark A. Lemley, *The (Unnoticed) Demise of the Doctrine of Equivalents*, 59 STAN. L. REV. 955 (2007); Lee Petherbridge, *On the Decline of the Doctrine of Equivalents*, 31 CARDOZO L. REV. 1371 (2010).

182. E.g., *Abraxis Biosci., Inc. v. Mayne Pharma (USA) Inc.*, 467 F.3d 1370, 1382 (Fed. Cir. 2006) (“[W]e conclude that the district court’s conclusion that Mayne’s generic propofol formulation infringes the patents in suit under the doctrine of equivalents was not clearly erroneous. The court correctly determined that [the infringer’s antimicrobial additive] calcium trisodium DTPA performs substantially the same function in substantially the same way to achieve the same result as [the patentee’s antimicrobial additive] edetate.”); *Boehringer v. Schering-Plough*, 320 F.3d 1339 (Fed. Cir. 2003) (finding of infringement even when evidence showed that the two viruses differed by at least seventy-three nucleotides and that the accused infringing virus exhibited substantial differences from the original); *Teva*, 876 F. Supp. 2d 295.

183. *But see* David L. Schwartz, *Explaining the Demise of the Doctrine of Equivalents*, 26 BERKELEY TECH. L.J. 1157, 1160 (2011) (reviewing Allison & Lemley, *supra* note 182, and Petherbridge, *supra* note 182). The author suggests that changes in patent litigation due to *Markman v. Westview Instruments*, 517 U.S. 370 (1996)—namely its holding that claim construction is a question of law for judges—has changed the focus of patent litigation to claim construction as a way to evaluate the reach of a claim. Schwartz concludes that, in consequence, the doctrine of equivalents has become a less important means of achieving this goal.

as enablement and obviousness, or questions of fact, such as the written description requirement. Although questions of fact are traditionally the purview of the jury, the questions often overlap, and a judge may make the ultimate decision.¹⁸⁴ There has been a trend to give judges more of this power, at least in some areas of patent law,¹⁸⁵ and it is not without reason.¹⁸⁶

However, it is not at all certain that shifting the burden of resolving patent issues onto the shoulders of lay judges is the best solution for resolving questions of scientifically complex material.¹⁸⁷ One proposal is that, if regular juries are not up to the task, the court should empanel juries of experts¹⁸⁸ or appoint a special master.¹⁸⁹ Another alternative could be to improve the role of the jury, perhaps by requiring special types of jury instructions in patent infringement cases. It is possible that the observed problems with juries simply stem from problems understanding their legal challenge, not their ability to comprehend the scientific material. If so, a carefully crafted special verdict form could preserve the value of the jury's analysis while still guiding and focusing its attention on resolving key findings, limiting instruction "to the core factual issues that control the ultimate verdict."¹⁹⁰

A final possibility is for patent law judges to embrace aspects of the FDA's regulatory determinations in evaluating biological similarity, when appropriate. As discussed above, biological similarity determinations are significant in analyses of obviousness and equivalence. Yet the legal system treats the FDA's findings inconsistently between these two legal conclusions. Patent courts take a very different approach in incorporating the FDA's regulatory determinations in analyzing obviousness than they do in analyzing equivalence. Regulatory bioequivalence has been acknowledged to play a role in some aspects of patentability, notably obviousness, where the Federal Circuit has recently stated that it is "most certainly relevant" to

184. For example, determining whether a patentee's acts constitute experimental use is technically a question of law, but it is a highly fact-intensive inquiry. The dissent in *Lough* argued that the heavy factual basis should be a reason to defer to the jury's findings. *Lough v. Brunswick Corp.*, 86 F.3d 1113, 1123 (Fed. Cir. 1996) (Plager, J., dissenting).

185. *E.g., Markman*, 517 U.S. 370 (holding claim construction to be a question of law).

186. The litigation between Centocor Biotech and Abbott Labs discussed *supra* Part I.B illustrates the sorts of problems or confusion that can emerge when lay juries confront highly technical or scientific material.

187. Besides promoting verdict uniformity, however, the benefits of allocating this task to judges, who are typically scientifically untrained, are unclear. Outside the context of patents, others have remarked upon how consolidating this power in the hands of these individuals can have uniformly unpleasant, not to mention scientifically unsound, outcomes. See Lisa Heinzerling, *Doubling Daubert*, 14 J.L. & POL'Y 65 (2006) for a good review.

188. This is White's solution: *see White, supra* note 165.

189. FED. R. CIV. P. 55.

190. *See Charles M. Cork, A Better Orientation for Jury Instructions*, 54 MERCER L. REV. 1 (2002).

that analysis.¹⁹¹ This is consistent with the low bar to patentability that obviousness poses.

In contrast, equivalence for the purposes of patent infringement litigation is distinct from regulatory bioequivalence,¹⁹² and patent courts have been historically reluctant to let the latter be determinative in the former's inquiry.¹⁹³ In determining whether two drugs are equivalent, the FDA is primarily interested in comparisons of their respective therapeutic safety and effectiveness.¹⁹⁴ In contrast, the doctrine of equivalents requires an "element-by-element" comparison of the claimed invention and the accused infringing product with respect to the drugs' functions, means, and results.¹⁹⁵ Although regulatory bioequivalence may not dispose of this inquiry, it is not entirely irrelevant.¹⁹⁶ For example, its inclusion is likely to depend upon how much of the biologic's therapeutic function is described in the patent claims.

Although some policy considerations underlying the separateness of these analyses are understandable,¹⁹⁷ the reasons for this continued separation are unclear, particularly in view of the biosimilar's "highly similar" requirements. As described in Part II.A–B, the FDA and its advisors make informed decisions about the similarity of drugs. They will soon be making further decisions about whether biologic drugs may be sufficiently functionally similar that they may be considered "highly similar." These conclusions,

191. See, e.g., *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1083 (Fed. Cir. 2012) ("At its core, Mylan and Par's proof of obviousness is that the claimed [pharmacokinetic] profile is bioequivalent to the immediate-release profile. In rejecting the sufficiency of Mylan and Par's proof, we do not hold that bioequivalence can never serve as evidence of obviousness. Indeed, it is most certainly relevant to that inquiry.").

192. See *Reckitt Benckiser Inc. v. Watson Labs., Inc.*, 430 F. App'x 871, 878 (Fed. Cir. 2011) ("[The Federal Circuit] clarified, however, that 'bioequivalency and equivalent infringement are different inquiries.'" (citing *Abbott Labs. v. Sandoz, Inc.*, 566 F.3d 1282, 1298 (Fed. Cir. 2009))); *Johns Hopkins Univ. v. Datascope Corp.*, 543 F.3d 1342, 1348 n.3 (Fed. Cir. 2008) ("[T]he jury may have concluded that the regulatory submission was evidence of equivalency, even though FDA equivalence is irrelevant to patent law because it involves fundamentally different inquiries.").

193. See, e.g., *Upjohn Co. v. Mova Pharm. Corp.*, 31 F. Supp. 2d 211, 215 n.2 (D.P.R. 1998) ("MOVA's admission of bioequivalence is not an admission of infringement under the doctrine of equivalents. They are two distinct concepts."), *aff'd in part, rev'd in part*, 225 F.3d 1306 (Fed. Cir. 2000).

194. *Abbott*, 566 F.3d at 1298 ("Bioequivalency is a regulatory and medical concern aimed at establishing that two compounds are effectively the same for pharmaceutical purposes.").

195. *Id.*

196. *Id.* ("While bioequivalency may be relevant to the function prong of the function-way-result test, bioequivalency and equivalent infringement are different inquiries. . . . Different attributes of a given product may thus be relevant to bioequivalency but not equivalent infringement, and vice versa.").

197. See *Abbott Labs. v. Sandoz, Inc.*, 486 F. Supp. 2d 767, 776 (N.D. Ill. 2007) ("If bioequivalency meant *per se* infringement, no alternative to a patented medicine could ever be offered to the public during the life of a patent.").

particularly when aided by the input of independent experts, have the potential to inform courts making decisions about similarity of biologics in the context of patent infringement, an entirely separate area. For example, the argument could be made that if a drug is sufficiently similar to a pioneer that it can use the accelerated pathway, this similarity should preclude its patentability altogether. Conversely, if the FDA were to find that a junior biologic was *not* highly similar, this finding could at least serve as a thumb on the scale in determining non-equivalence.

Another area in which FDA analyses could influence patent-related decisions concerns the use of postmarket safety or clinical data, because much information about a biologic's effects only becomes available once patients have widely used the drug. For applications filed before March 16, 2013,¹⁹⁸ however, obviousness is measured from the time of the invention, so postmarket safety data would likely be irrelevant to the obviousness inquiry—and this is unlikely to change when the time for measuring obviousness shifts to the filing date. It is not clear why postmarket safety data could not be used for analyses of equivalence though, particularly when the analysis focuses upon the “function” prong, since the doctrine of equivalents has no evident timing requirement. If these data were permissible, an alleged infringer could produce postmarket information to show functional differences in his product and consequently avoid a finding of equivalence.

E. *Making the Decisions: Choices for Manufacturers*

The above discussion highlights significant regulatory and patenting concerns facing the manufacturers of biologic therapeutics. As these organizations decide where and how to allocate their research and development resources, however, other concerns are also pertinent and worth mentioning.

From an economic perspective, the development of biologics and biosimilars may be a questionable investment. It represents an enormous investment of time and money, yet this investment may only yield diminishing returns.¹⁹⁹ Although Humira, Enbrel, and Remicade have achieved significant market presence and enormous financial returns, there are other TNF α inhibitors that have not attained their clout—yet.²⁰⁰ Thus, development of more TNF α inhibitors represents a gamble: a roll of the dice to yield a

198. The America Invents Act revision of 35 U.S.C. § 103 changes the time of obviousness inquiry to the time that the application was filed, taking effect for applications filed after March 16, 2013. Leahy-Smith America Invents Act, Pub. L. No. 112-29, § 3(c), 125 Stat. 284 (2011).

199. See, e.g., McCamish, *supra* note 98, at 212. (“[I]n order to be viable as a business, a [biosimilar] sponsor must also ensure their development is efficient by receiving product approval in a timely manner and with lower costs than those required for development of a novel agent.”).

200. For example, certolizumab pegol and golimumab, described in Aaltonen et al., *supra* note 37, at 11.

Humira clearly justifies the investment, but this kind of success cannot likely be predicted from the outset. This success heavily depends on another factor: decision making on the part of physicians, who must choose to prescribe one drug over another. Because doctors consider the efficacy, cost, safety, and any special advantages of any particular drug,²⁰¹ it may be worthwhile for manufacturers to invest in comparative effectiveness research. These economic concerns should not necessarily constitute deal breakers. Even when several similar biologics are available, the TNF α inhibitors demonstrate that multiple members of one family may prove individually quite lucrative, particularly when the target disease affects great numbers of the population, and the duration of illness is substantial.

For pharmaceutical manufacturers concerned with civic or social responsibility, it is also important to consider the impact of biologic and biosimilar development on society at large. In particular, biosimilars exist to treat the same mechanisms as preexisting pioneer drugs, though presumably at lower cost.²⁰² Accordingly, their function is largely redundant, and a comparable argument can be made even for the similar-impact biologics. Creation of multiple TNF α inhibitors may preclude development of other useful means of treating the target disease. In the etiology of RA, although TNF α -TNFR signaling is an important player, it is by no means the only one,²⁰³ and other molecules cause the inflammation characteristic of RA.²⁰⁴ Thus, one reasonable alternative strategy for pharmaceutical manufacturers is to pursue drugs against other targets in the same compromised molecular pathway, if applicable. In the case of RA, biological therapeutics have been developed against such targets.²⁰⁵

Further, when pharmaceutical manufacturers expend their efforts to develop similar drugs for common diseases, they divert human and financial resources away from other socially useful avenues, such as developing treatments for other diseases where the market is less saturated with competition. This allocation of resources precludes the development of drugs for other diseases, when that development would be less lucrative for the manufactur-

201. See Philip J. Mohler, *New Drugs: How to Decide Which Ones to Prescribe*, 13 *FAM. PRACTICE MGMT.* 33, 34 (2006), available at <http://www.aafp.org/fpm/2006/0600/p33.html> (“Scrutinize new drugs that end with XL, CR, ER, SR or XR. Does the drug offer clinically relevant new efficacy, safety or adherence benefits, or is it simply a ‘me too’ product?”).

202. See Liang, *supra* note 7, at 416 (arguing that biosimilars will primarily be of interest to those with financial constraints, as generics). However, if they are introduced only after expiry of the reference drug patent and its market monopoly, it is not clear why the price of one should differ from the price of the other.

203. See Sandeep K. Agarwal, *Biologic Agents in Rheumatoid Arthritis: An Update for Managed Care Professionals*, 17 *J. MANAGED CARE PHARMACY (SUPP.)* S14 (2011), available at <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=13697>.

204. See *id.* at S14 (noting the roles of interleukins-1 and -6 and various proteases).

205. See *id.* at S16 (describing rituximab, a B-cell inactivating antibody, and tocilizumab, an antibody against the interleukin-6 receptor). Rituximab is actually gaining popularity as a backup treatment when other TNF α inhibitor therapy fails.

ers. For example, many people suffer from “orphan” diseases, for which no effective drug has yet been developed, and they would greatly benefit from pharma’s investment.²⁰⁶ Finally, others have worried about possible harm posed by biosimilar drugs to especially vulnerable populations.²⁰⁷ While these concerns are valid, it is not apparent that they pertain to biosimilars more than they would pertain to any drug that treats a serious disease.

Perhaps the strongest argument in favor of focusing upon similar-impact biologic development is that when a great number of persons suffer from the same disease, the need for a cure is proportionately large. Given the physiological variability of these patients, a banquet of similar treatment options may be extremely valuable. The TNF α inhibitor data illustrate that many patients may be unresponsive to one of the drugs, and the cited studies suggest that patients are likely to derive a very strong health benefit from being able to switch between available similar therapeutics, if one performs better for them personally or has fewer attendant side effects.

A final consideration is that a heightened research focus on similar molecules may advance knowledge in the relevant field, but at the expense of more novel, non-translational studies. Yet the types of different clinical effects described above observed for similar biologics do illustrate the nature of biological complexity, and the commercial availability of these drugs spurs research by interested clinicians and academics.

CONCLUSION

Despite the risks described above, it seems certain that many pharmaceutical manufacturers will opt to invest in developing similar biologics or biosimilar therapeutics. Increased awareness of and attention to the scientific, regulatory, and legal challenges facing their products is certain to help these companies achieve the greatest return on their investment. Ultimately, these efforts will redound to the benefit of patients anxious for relief.

206. See George J. Brewer, *Drug Development for Orphan Diseases in the Context of Personalized Medicine*, 154 *TRANSLATIONAL RES.* 314, 314 (2009). Brewer notes that a drug must service at least 200,000 patients in order for the manufacturer to turn a profit.

207. See Liang, *supra* note 7, at 416 (arguing that, due to their capability to treat serious diseases, harm resulting from their unknown and unpredictable effects can fall disproportionately on those with the greatest health concerns). For each disease cited, there are other available drugs, each with their own attendant risks, which may be greater than any risk posed by a biosimilar.