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ABSTRACT

This Article fills a gap in the literature by conducting a comprehensive analysis of patent infringement in the context of follow-on biologics. Patent infringement is an important topic because, like small molecule generic drugs, follow-on biologics are likely to begin their life facing infringement suits. Because it is tremendously expensive to develop a follow-on biologic, it is vital that there be consistency in how they are treated in the courts once the inevitable patent infringement suits arrive. If follow-on biologics companies cannot predict how their product will be received in court, they may decide it is not worth the risk to develop the product. This Article looks at types of strategies industry is likely to use to avoid infringement and how courts are likely to respond to these strategies. This Article focuses predominantly on the doctrine of equivalents, both because it will be particularly important in suits concerning follow-on biologics (it is nearly impossible to make a follow-on biologic identical to the reference drug) and because it represents the outer limits of the scope of a patent, and thus the most difficult cases. The Article is important for courts that must create a coherent body of law where no precedent yet exists, for industry members trying to predict how their products will be received and for policy makers who seek to understand the nature of infringement suits and shape this body of law in a

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direction that makes sense for all parties involved.

INTRODUCTION

Follow-on biologics[1] have attracted a great deal of attention, first as a conceptual matter, and then as a practical matter in the wake of the 2009 Biologics Price Competition and Innovation Act (BPCIA) which created a pathway for "generic" biologics.[2] The literature contains in-depth coverage of questions of proper legislative design,[3] whether follow-on biologics will be safe and effective,[4] and how a pathway for follow-on biologics will affect

1. Alternatively called follow-on protein products and subsequent entry biologics.

2. 42 U.S.C. § 262(i)(2) (West 2012).

3. Brian R. Bouggy, *Follow-On Biologics Legislation: Striking a Balance Between Innovation and Affordability*, 7 IND. HEALTH L. REV. 367 (2010); Tam Q. Dinh, *Potential Pathways for Abbreviated Approval of Generic Biologics under Existing Law and Proposed Reforms to the Law*, 62 FOOD & DRUG L.J. 77, 81 (2007); Michael P. Dougherty, *The New Follow-On-Biologics Law: A Section by Section Analysis of the Patent Litigation Provisions in the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 231 (2010); Donna M. Gitter, *Innovators and Imitators: An Analysis of Proposed Legislation Implementing an Abbreviated Approval Pathway for Follow-on Biologics in the United States*, 35 FLA. ST. U. L. REV. 555 (2008); Ingrid Kaldre, *The Future of Generic Biologics: Should the United States "Follow-on" the European Pathway?*, 2008 DUKE L. & TECH. REV. 1 (2008); Kathleen Kelleher, Note, *FDA Approval of Generic Biologics: Finding a Regulatory Pathway*, 14 MICH. TELECOMM. & TECH. L. REV. 245, 261-63 (2007); Alana Montas, *Cheaper Clinical Trials: The Real Solution to the Biologic Industry's Gordian Knot*, 37 AM. J.L. & MED. 172 (2011); Jordan Paradise, Foreword, *Follow-On Biologics: Implementation Challenges and Opportunities*, 41 SETON HALL L. REV. 501 (2011); Sarah Sorscher, *A Longer Monopoly for Biologics?: Considering the Implications of Data Exclusivity as a Tool for Innovation Policy*, 23 HARV. J.L. & TECH. 285 (2009-2010); Joyce Wing Yan Tam, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J. 535, 558-62 (2010); Linfong Tzeng, *Follow-on Biologics, Data Exclusivity, and the FDA*, 25 BERKELEY TECH. L.J. 135 (2010); Dawn Willow, *The Regulation of Biologic Medicine: Innovators' Rights and Access to Healthcare*, 6 J. INTELL. PROP. 32, 34 (2006).

4. Lisa D. DiMartino et al., *Using Medicare Administrative Data to Conduct*

brand-name incentives to innovate.[5] However, the literature contains no comprehensive treatment of patent infringement in the context of follow-on biologics.

Patent infringement is an important topic because, like small molecule generic drugs, follow-on biologics are likely to begin their life facing infringement suits. The BPCIA sets up complex procedures for resolving patent disputes prior to entry.[6] Although follow-on biologics will not enter the market until after expiration of the core (new biological entity) patent covering the reference drug, the reference drug will still be covered by a variety of weaker patents protecting matters such as manufacturing processes, formulation or packaging.[7] Because the BPCIA requires follow-on biologics to be "highly similar to the reference product," there is the potential for patent conflict every time a follow-on biologic enters the market.

Once the first follow-on biologic infringement suit is filed, courts will have the grueling task of sorting through the science to apply it to a body of law invented long before the elemental discoveries of biotechnology even happened, much less understood. Unfortunately, courts do not have the luxury of muddling through early cases and creating conflicting standards before eventually settling into a more coherent body of law with the help of the Federal Circuit. Courts need to create a coherent body of law right from the beginning. It is tremendously expensive to develop a follow-on biologic, so it is

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Postmarketing Surveillance of Follow-On Biologics: Issues and Opportunities, 63 FOOD & DRUG L.J. 891 (2008); Elysa B. Goldberg, *Fixing a Hole: Will Generic Biologics Find a Niche Within the Hatch-Waxman Act*, 20 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 327, 331 (2010); Megan Thisse, *Working the Bugs out of Biologics: A Look at the Access to Life-Saving Medicines Act and Follow-On Biologics*, 18 ALB. L.J. SCI. & TECH. 543 (2008); Jeanne Yang, *A Pathway to Follow-On Biologics*, 3 HASTINGS SCI. & TECH. L.J. 217, 220 (2011); Joshua Boger, *Follow-on Biologics: Balancing Innovation and Cost Savings*, Health Care Cost Monitor (Nov.12, 2009), http://healthcarecostmonitor.thehastingscenter.org/joshuaboger/follow-on-biologics-balancing-innovation-and-cost-savings.

5. Katherine N. Addison, *The Impact of the Biosimilars Provision of the Health Care Reform Bill on Innovation Investments*, 10 J. MARSHALL REV. INTELL. PROP. L. 553 (2011); Yaniv Heled, *Patents vs. Statutory Exclusivities in Biological Pharmaceuticals—Do We Really Need Both?*, 18 MICH. TELECOMM. & TECH. L. REV. 419 (2012); Jeremiah J. Kelly, *Follow-on Biologics: Legal, Scientific, and Policy Considerations*, 13 J. HEALTH CARE L. & POL'Y 257, 257 (2010); Jeremiah J. Kelly & Michael David, *No Longer "If," But "When": The Coming Abbreviated Approval Pathway for Follow-on Biologics*, 64 FOOD & DRUG L.J. 115, 138-40 (2009); Maxwell R. Morgan, *Regulation of Innovation Under Follow-On Biologics Legislation: FDA Exclusivity As An Efficient Incentive Mechanism*, 11 COLUM. SCI. & TECH. L. REV. 93 (2010); John A. Vernon et al., *Exploration of Potential Economics of Follow-on Biologics and Implications for Data Exclusivity Periods for Biologics*, 16 B.U. J. SCI. & TECH. L. 55 (2010).

6. *See generally* 42 U.S.C. § 262 (2010).

7. Although the BPCIA contains anti-evergreening provisions intended to curb some of the strategic patenting seen in generic drugs, biologics are still likely to be covered by a broad patent portfolio to give them maximum protection against follow-on biologics. *See infra* Part II.

vital that there be consistency in how they are treated in the courts once the inevitable patent infringement suits arrive. If follow-on biologics companies cannot predict how their product will be received in court, they may decide it is not worth the risk to create it.

A product may infringe either literally, meaning that the accused product copies every detail of the patent, or by equivalents, meaning that there are "insubstantial differences" between the products.[8] A product infringes by equivalents if it does "the same work in substantially the same way[s] and accomplish[es] substantially the same result" even if it "differ[s] in name, form, or shape."[9]

Relative to other types of products, literal infringement is likely to be somewhat less important in the context of follow-on biologics. This is because it is incredibly difficult—perhaps impossible—for the follow-on biologic to be identical to the reference drug.[10] While arguing against the creation of a follow-on biologic pathway, the brand-name industry itself stated that "[t]o achieve identical composition between biologics produced by unrelated manufacturers is virtually impossible because of the nature of biological manufacturing."[11] While this does not mean that a follow-on biologic cannot literally infringe, it does suggest that literal infringement will be a more challenging argument. Therefore the doctrine of equivalents will likely be of outsized importance in infringement litigation concerning follow-on biologics.[12]

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8. Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co., 520 U.S. 17, 19 (1997).

9. Union Paper-Bag Mach. Co. v. Murphy, 97 U.S. 120, 125 (1877).

10. This has led to several articles suggesting that the difficulty in replicating biologics might mean that the patents covering biologics are not properly enabled and thus invalid. Dmitry Karshtedt, *Limits on Hard-to-Reproduce Inventions: Process Elements and Biotechnology's Compliance with the Enablement Requirement*, 3 HASTINGS SCI. & TECH. L.J. 109 (2011); Gregory N. Mandel, *The Generic Biologics Debate: Industry's Unintended Admission that Biotech Patents Fail Enablement*, 11 VA. J.L. & TECH. 11, 1 (2006); Joyce Wing Yan Tam, *Biologics Revolution: The Intersection of Biotechnology, Patent Law, and Pharmaceutical Regulation*, 98 GEO. L.J. 536, 544-47 (2010).

11. Memorandum from the Pharm. Research and Mfrs. of Am. to the Food and Drug Admin. (Nov. 12, 2004), http://www.fda.gov/ohrms/dockets/dockets/04n0355/04n-0355-c000004-01-vol1.pdf.

12. Courts and scholars have recognized that the science of biotechnology makes it uniquely challenging to apply the doctrine of equivalents to biotechnology. *See, e.g.*, Lawrence S. Graham, *Equitable Equivalents: Biotechnology and the Doctrine of Equivalents After* Warner-Jenkinson Co. v. Hilton Davis Chemical Co., 6 J.L. & POL'Y 741, 777-85 (1997-1998) (arguing that the doctrine of equivalent is not readily applied to biotechnology and providing several examples of cases where it is inappropriate); Qing Lin, *A Proposed Test for Applying the Doctrine of Equivalents to Biotechnology Inventions: The Nonobviousness Test*, 74 WASH. L. REV. 885, 900 (1999) (arguing that the doctrine of equivalents is difficult to apply to biotechnology because scientists often do not understand the "way" in which a biotechnology product works, and therefore cannot provide enough evidence to fulfill the "way" requirement). *See also Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555, 1570 (Fed. Cir. 1994) (Lourie, J., concurring) (explaining some of the difficulties in applying the doctrine of equivalents to the case at hand). However, the

This Article fills a gap in the literature by conducting a comprehensive analysis of infringement in the context of follow-on biologics. I look both at the types of strategies that follow-on biologics companies are likely to use to avoid infringement, and how courts are likely to respond to these strategies. I focus predominantly on the doctrine of equivalents, both because it represents the outer limits of the scope of a patent, and thus the most difficult cases, and because it will be particularly important in suits concerning follow-on biologics. I find that it will be easiest for follow-on biologics to make changes at certain stages of the manufacturing process where the BPCIA and FDA regulations give them more latitude to stray from the precise form of the brand-name product. These less regulated areas give follow-on biologics companies greater scope to make changes that will bring them outside the range of equivalents for the brand-name product.

The Article is important for courts that must create a coherent body of law where no precedent yet exists. It is important for policy makers and scholars who seek to understand the nature of follow-on biologics infringement suits and how to shape this body of law in a direction that makes sense for the ultimate stakeholder: the patient.

In Part I, I give a brief explanation of patent infringement, with an emphasis on the doctrine of equivalents, because it defines the outer border of patent protection. In Part II, I define "biologics," explain how they differ from small molecule drugs, and describe the history of biologics regulation world-wide, in particular the history of the BPCIA. I next summarize the follow-on biologics that have been approved in Europe, and what changes those follow-on biologics have made from the innovator drug. I summarize the FDA regulations governing follow-on biologics and what they mean for types of work-arounds that follow-on biologics will be permitted to attempt.

In Part III, I explore how the BPCIA and patent law will shape infringement suits. I draw my conclusions from the interaction between patent law and the BPCIA, which make certain types of infringement more likely, from infringement cases involving biotechnology (not follow-on biologics, as none have been brought—yet) and from doctrine of equivalents suits that have been brought for generic small molecule drugs. I then make policy suggests for how courts should treat these cases when they inevitably begin arriving on dockets across the country.

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doctrine of equivalents has been applied to numerous biotechnology cases, suggesting that courts will continue attempting to apply it in the context of follow-on biologics. *See, e.g.*, Amgen Inc. v. Hoffmann-La Roche Ltd., 580 F.3d 1340 (Fed. Cir. 2009); Carnegie Mellon University v. Hoffmann-La Roche Inc., 541 F.3d 1115 (Fed. Cir. 2008); Boehringer Ingelheim Vetmetica, Inc. v. Schering-Plough Corp., 320 F.3d 1339 (Fed. Cir. 2003); Genentech, Inc. v. Boehringer Mannheim GmbH, 47 F. Supp. 2d 91 (D. Mass. 1999).

I. PATENT LAW AND THE DOCTRINE OF EQUIVALENTS

Patents "promote the Progress of Science and useful Arts"[13] by granting property rights in information in exchange for full disclosure of the invention.[14] However, patent law exists in a careful balance. If inventors receive too little reward for their invention, innovation will decrease. If inventors receive too much reward for their invention, their monopoly rights prevent secondary innovation[15] and may prevent optimal public use.[16]

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13. U.S. CONST. art. I, § 8, cl. 8.

14. *See, e.g.*, Graham v. John Deere Co. of Kan. City, 383 U.S. 1, 9 (1966) ("The patent monopoly was not designed to secure to the inventor his natural right in his discoveries. Rather, it was a reward, an inducement, to bring forth new knowledge."); Mazer v. Stein, 347 U.S. 201, 219 (1954) ("The economic philosophy behind the clause empowering Congress to grant patents and copyrights is the conviction that encouragement of individual effort by personal gain is the best way to advance public welfare through the talents of authors and inventors in 'Science and useful Arts.'"). *See also* Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575, 1576 (2003) ("Patent law is our primary policy tool to promote innovation, encourage the development of new technologies, and increase the fund of human knowledge."); Mark A. Lemley & David McGowan, *Legal Implications of Network Economic Effects*, 86 CALIF. L. REV. 479, 526 (1998) ("Indeed, the principle behind intellectual property law is that competition should be sacrificed to some extent in order to give sufficient incentive for innovation."); Lawrence Lessig, *Intellectual Property and Code*, 11 ST. JOHN'S J. LEGAL COMMENT. 635, 638 (1996) ("while we protect real property to protect the owner from harm, we protect intellectual property to provide the owner sufficient incentive to produce such property.").

15. *See, e.g.*, Jonathan M. Barnett, *Cultivating the Genetic Commons: Imperfect Patent Protection and the Network Model of Innovation*, 37 SAN DIEGO L. REV. 987, 1000 (2000) ("Today academic and industrial researchers commonly lament the ballooning costs of navigating around proliferating clusters of patent claims, and some commentators contend that patent claims ultimately will result in upstream strangleholds on basic-research discoveries that will significantly impede downstream technological applications."); Michael A. Carrier, *Resolving the Patent-Antitrust Paradox Through Tripartite Innovation*, 56 VAND. L. REV. 1047, 1081-85 (2003) (explaining how patents can interfere with cumulative innovation); Michael A. Heller & Rebecca S. Eisenberg, *Can Patents Deter Innovation? The Anticommons in Biomedical Research*, 280 SCI. 698, 698 (1998) (arguing in the context of biomedical research that patent holders can impede downstream research); Lisa Mandrusiak, *Balancing Open Source Paradigms and Traditional Intellectual Property Models to Optimize Innovation*, 63 ME. L. REV. 303, 310-11 (2010) (providing an overview of the anticommons patent problem); Robert P. Merges & Richard R. Nelson, *On the Complex Economics of Patent Scope*, 90 COLUM. L. REV. 839, 843 (1990). However, some scholars have argued that the original inventor is in the best position to develop and coordinate downstream innovation. *See* Edmund W. Kitch, *The Nature and Function of the Patent System*, 20 J.L. & ECON. 265, 276-77 (1977).

16. Optimal public use is demonstrated by charging inflated prices for the product, which increases prices for consumers. *See* Note, *Limiting the Anticompetitive Prerogative of Patent Owners: Predatory Standards in Patent Licensing*, 92 YALE L.J. 831, 836 (1983) ("The patent system . . . reflects a tradeoff between dynamic and static efficiency.").

A related problem is the recent rise of patent trolls. For more information on the problem of patent trolls, *see, e.g.,* Einer Elhauge, *Do Patent Holdup and Royalty Stacking Lead to Systematically Excessive Royalties?*, 4 J. COMPETITION L. & ECON. 535, 537 (2008); Damien Geradin et al., *The Complements Problem Within Standard Setting: Assessing the*

A patent is made up of two main parts: the specification and the claims.[17] The specification is a narrative description of the invention, while the claims define the boundaries of the patent. Historically, claims were not required in a patent, which consisted only of a description of the invention in the specification.[18] Courts interpreting the patent looked at the specification to determine the "essence" of the patent[19] in order to answer fuzzy questions about the "similarity" of the inventions.[20] The specification-only system worked poorly.[21] Because the specification did not clearly define the bounds of the patent, it was nearly impossible for either the patentee or the public to determine exactly where those boundaries were located.[22]

Claims were first statutorily required in the Patent Act of 1870.[23] Claims define the bounds of the patent's scope.[24] Claims also serve a public notice

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Evidence on Royalty Stacking, 14 B.U. J. SCI. & TECH. L. 144, 145 (2008); John M. Golden, Commentary, "*Patent Trolls" and Patent Remedies*, 85 TEX. L. REV. 2111, 2145-47 (2007); J. Gregory Sidak, *Holdup, Royalty Stacking, and the Presumption of Injunctive Relief for Patent Infringement: A Reply to Lemley and Shapiro*, 92 MINN. L. REV. 714, 714 (2008). However, note that the negative view of patent trolls is not unanimous. Some think that they provide a useful economic function. *See, e.g.*, Sannu K. Shrestha, *Trolls or Market-Makers? An Empirical Analysis of Nonpracticing Entities*, 110 COLUM. L. REV. 114, 115-16 (2010) (suggesting that patent trolls enhance innovation by serving a sort of venture capital role to capital-poor inventors by creating a market for patents and inventions). *See also* James F. McDonough III, Comment, *The Myth of the Patent Troll: An Alternative View of the Function of Patent Dealers in an Idea Economy*, 56 EMORY L.J. 189, 190 (2006) ("[T]rolls act as a market intermediary in the patent market. Patent trolls provide liquidity, market clearing, and increased efficiency to the patent markets—the same benefits securities dealers supply capital markets.").

17. 35 U.S.C. § 112 (2006).

18. Christopher A. Cotropia, *Patent Claim Interpretation Methodologies and Their Claim Scope Paradigms*, 49 WM. & MARY L. REV. 49, 63 (2005) (explaining that the 1793 patent statute did not require a claim).

19. Odiorne v. Winkley, 18 F. Cas. 581, 582 (C.C.D. Mass. 1814) (No. 10,432).

20. Keystone Bridge Co. v. Phoenix Iron Co., 95 U.S. 274, 278 (1877).

21. John F. Duffy, *The Festo Decision and the Return of the Supreme Court to the Bar of Patents*, 2002 SUP. CT. REV. 273, 309 (2002) (Noting that "lay jurors would find no infringement because they would see many superficial differences between the defendant's machine and the description of the patented invention and thus believe the two not substantially identical.").

22. Cotropia, *supra* note 18, at 63.

23. Act of July 8, 1870, § 26, 16 Stat. 201 (the patent must "particularly point out and distinctly claim" the invention).

24. *See, e.g.*, Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 234 F.3d 558, 622 (Fed. Cir. 2000) ("In drafting an original claim of a patent application, the writer sets out the metes and bounds of the invention . . ."); Markman v. Westview Instruments, Inc., 52 F.3d 967, 1000 (Fed. Cir. 1995) ("The legal effect of the patent claim is to establish the metes and bounds of the patent right to exclude . . ."); Zenith Labs., Inc. v. Bristol-Myers Squibb Co., 19 F.3d 1418, 1424 (Fed. Cir. 1994) ("It is the claim that sets the metes and bounds of the invention entitled to the protection of the patent system."); Corning Glass Works v. Sumitomo Elec. U.S.A., Inc., 868 F.2d 1251, 1257 (Fed. Cir. 1989) ("A claim in a patent provides the metes and bounds of the right which the patent confers on the patentee to exclude others from making, using or selling the protected invention.").

function, giving third parties notice of the existence of the claim and the location of the boundaries.[25] Claims can then be used by competitors as a guide to designing around the patent.[26] The Supreme Court promotes using claims to develop work-arounds, stating, for example, that claims "inform the public during the life of the patent of the limits of the monopoly asserted, so that it may be known which features may be safely used or manufactured without a license and which may not."[27]In an infringement suit, the court begins by inquiring as to whether a claim has been literally infringed, meaning that the defendant has copied every detail of the claim.[28] However, the Supreme Court worried that restricting patent protection to cases where the defendant literally infringed would make it simple for an "unscrupulous copyist to make unimportant and insubstantial changes and substitutions in the patent[,]"[29] which would greatly diminish the value of the patent.[30]

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25. PSC Computer Prods., Inc. v. Foxconn Int'l, Inc., 355 F.3d 1353, 1359 (Fed. Cir. 2004) ("[C]laims serve the important notice function of informing the public that anyone who makes, uses, or sells the claimed invention infringes the patent.").

26. *See, e.g.*, Read Corp. v. Porter, Inc., 970 F.2d 816, 828 (Fed. Cir. 1992) ("We have often noted that one of the benefits of the patent system is the incentive it provides for 'designing around' patented inventions, thus creating new innovations."); Slimfold Mfg. v. Kinkead Indus., 932 F.2d 1453, 1457 (Fed. Cir. 1991) ("Designing around patents is, in fact, one of the ways in which the patent system works to the advantage of the public in promoting progress in the useful arts, its constitutional purpose."); State Indus., Inc. v. A.O. Smith Corp., 751 F.2d 1226 (Fed. Cir. 1985) ("One of the benefits of a patent system is its so-called "negative incentive" to "design around" a competitor's products, even when they are patented, thus bringing a steady flow of innovation to the marketplace. It should not be discouraged . . ."). However, courts do not always regard designing-around as a benefit of the patent system. *See, e.g.*, Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 607 (1950) (concerned that allowing too much design-around would "covert the protection of the patent grant into a hollow and useless thing."). *See also* Tun-Jen Chiang, *The Levels of Abstraction Problem in Patent Law*, 105 NW. U. L. REV. 1097, 1138 (2011) (arguing that if the patent's scope were "confined to precise replication . . . , then pirates would quickly learn to copy the principle or the heart of the patent without replicating the precise embodiment . . . [.] [P]rotection limited to literal reproduction is worthless and easily circumvented.").

27. Permutit Co. v. Graver Corp., 284 U.S. 52, 60 (1931).

28. *Graver Tank*, 339 U.S. at 607.

29. *Id. See also* Tun-Jen Chiang, *The Levels of Abstraction Problem in Patent Law*, 105 NW. U. L. REV. 1097, 1138 (2011) (explaining the importance of the doctrine of equivalents). *But see* Timothy R. Holbrook, *Equivalency and Patent Law's Possession Paradox*, 23 HARV. J.L. & TECH. 1, 39 (2009) (pointing out that the doctrine of equivalents may be responsible for decreasing a patentee's incentive for downstream innovation because if there was no doctrine of equivalents, patentees would have an incentive to "continue to innovate and improve upon her invention because others will have the opportunity to invent and patent improvements on it."); Lee Petherbridge, *On the Decline of the Doctrine of Equivalents*, 31 CARDOZO L. REV. 1371, 1404 (2010) (noting that courts are increasingly reluctant to rule for plaintiffs on doctrine of equivalents grounds but that "[a]mple evidence suggests that all the while the courts were killing the doctrine of equivalents, patent applicants were increasing the rate at which they filed applications for new inventions.").

30. Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 731 (2002) ("If patents were always interpreted by their literal terms, their value would be greatly

The Court therefore expanded the scope of the monopoly that patentees could claim by creating the equitable doctrine of equivalents.[31] The doctrine of equivalents expands the patentee's right to exclude beyond the fence created by the literal meaning of the claims to include inventions that perform "substantially the same function in substantially the same way to obtain the same result."[32] The intent is to prevent a competitor from committing a "fraud on a patent"[33] by creating a product that is functionally identical to the patented product and thus should equitably fall within the patent's scope.

Infringement under the doctrine of equivalents can be decided using one of two tests. The "function-way-result" test asks whether the defendant's device functions substantially the same way to achieve substantially the same result.[34] The "insubstantial differences" test asks whether the defendant's device is substantially different from the patent scope.[35] The Supreme Court has expressed no preference between the tests, stating that the "particular linguistic framework used [to determine equivalency] is less important than whether the test is probative of the essential inquiry."[36]

Equivalency is a question for the jury[37] although in practice it is often decided on summary judgment.[38] An inquiry into equivalence is fact-heavy and must consider "the context of the patent, the prior art, and the particular circumstances of the case. Equivalence . . . is not the prisoner of a formula and is not an absolute to be considered in a vacuum."[39] The Supreme Court also instructs juries to consider "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."[40] In fields involving quickly developing technology, the doctrine protects patentees from "'after-arising' technology because a patent draftsman has no way to anticipate and account for later developed

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diminished.").

31. The doctrine of equivalents first appeared in Supreme Court jurisprudence in *Winans v. Adams*, 56 U.S. 330 (1853).

32. Graver Tank & Mfg. Co. v. Linde Air Prods. Co., 339 U.S. 605, 608 (1950) (quoting Sanitary Refrigerator Co. v. Winters, 280 U.S. 30, 42 (1929)).

33. *Graver Tank*, 399 U.S. at 608.

34. *Sanitary Refrigerator Co.*, 280 U.S. at 42.

35. Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 39 (1997).

36. *Id.* at 40.

37. *Graver Tank*, 399 U.S. at 609.

38. Allison & Lemley suggest that the doctrine of equivalents has been in decline since *Markman* made claim construction a matter of law. Because courts now resolve questions of claim construction as a matter of law, they are incentivized to resolve the entire matter on summary judgment to avoid a trial. Thus if they make a finding on literal infringement as a matter of law, they are likely to do the same for infringement under the doctrine of equivalents. John R. Allison & Mark A. Lemley, *The (Unnoticed) Demise of the Doctrine of Equivalents*, 59 STAN. L. REV. 955, 977 (2007).

39. *Graver Tank*, 339 U.S. at 609.

40. *Id.*

substitutes for a claim element."[41] Whether the accused product is patented is relevant, but not dispositive.[42]

The doctrine of equivalents is controversial.[43] Part of the controversy—both scholarly and judicial—arises because the doctrine creates an inherent tension between its goal of protecting patent rights and its unintended consequence of increasing uncertainty and reducing the clarity of patents.[44] Patents, like any property right, function best when they clearly delineate the boundaries of the property, enabling other parties to invest and invent around those boundaries with confidence that they are not infringing. On one hand, the doctrine of equivalents reflects courts' desire to ensure patent protection is broad enough that inventors have an incentive to innovate and to publically disclose their inventions.[45] However, by extending a patent's boundaries to

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41. Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1320 n.2 (Fed. Cir. 1999). *See also* Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc., 145 F.3d 1303, 1310 (Fed. Cir. 1998) ("Due to technological advances, a variant of an invention may be developed after the patent is granted, and that variant may constitute so insubstantial a change from what is claimed in the patent that it should be held to be an infringement.").

42. Federal Circuit jurisprudence is imprecise on the importance of this factor. In *Hoechst Celanese Corp. v. BP Chems. Ltd.*, the Federal Circuit held that the accused product's "patentability presents no legal or evidentiary presumption of noninfringement." 78 F.3d 1575, 1582 (Fed. Cir. 1996). The fact that the defendant's device is patented over the plaintiff's device does not preclude a finding that the defendant's device infringes by equivalents. Roton Barrier, Inc. v. Stanley Works, 79 F.3d 1112, 1128 (Fed. Cir. 1996) (Nies, J., concurring). However, if an accused product is patented, the USPTO must have determined that the accused product did not read onto the plaintiff's patent, which would have been prior art. In *Hoganas AB v. Dresser* Indus., the Federal Circuit noted that the defendant had obtained a patent covering their product, and that the plaintiff's patent was listed as art of record for the defendant's product, but that the USPTO had nevertheless granted the defendant's patent. 9 F.3d 948, 954 (Fed. Cir. 1993).

43. Michael J. Meurer & Craig A. Nard, *Innovation, Refinement and Patent Claim Scope: A New Perspective on the Doctrine of Equivalents*, 93 GEO. L.J. 1947, 1948 (2005); Lee Petherbridge, *On the Decline of the Doctrine of Equivalents*, 31 CARDOZO L. REV. 1371, 1372 (2010). *See also* Martin J. Adelman and Gary L. Francione, *The Doctrine of Equivalents in Patent Law: Questions that Pennwalt Did Not Answer*, 137 U. PENN. L. REV. 673 (1989); Joseph S. Cianfrani, *An Economic Analysis of the Doctrine of Equivalents*, 1 VA. J.L. & TECH. 1 (1997); Paul R. Michel, *The Role and Responsibility of Patent Attorneys in Improving the Doctrine of Equivalents*, 40 IDEA 123 (2000); Joshua D. Sarnoff, *Abolishing the Doctrine of Equivalents and Claiming the Future after Festo*, 19 BERK. TECH. L.J. 1157 (2004); John R. Thomas, *Claim Re-Construction: The Doctrine of Equivalents in the Post-Markman Era*, 9 LEWIS & CLARK L. REV. 153 (2005); T. Whitley Chandler, *Prosecution History Estoppel, the Doctrine of Equivalents, and the Scope of Patents*, 13 HARV. J.L. & TECH. 465 (2000).

44. *E.g.*, Warner-Jenkinson Co. v. Hilton Davis Chem. Co., 520 U.S. 17, 29 (1996) ("[T]he doctrine of equivalents, when applied broadly, conflicts with the definitional and public-notice functions of the statutory claiming requirement."); D. Alan White, *The Doctrine of Equivalents: Fairness and Uncertainty in an Era of Biologic Pharmaceuticals*, 60 EMORY L.J. 751, 773 (2011); Petherbridge, *supra* note 43, at 1374.

45. White, *supra* note 44, at 756. Petherbridge suggests that the doctrine of equivalents bolsters the patent system because innovators might be reluctant to make new inventions if competitors could get around their patent by making minor changes to the product. *Supra*

inventions not literally within the bounds of the claims, the doctrine increases uncertainty and may deter investment and business activities.[46]

It is unclear how this problem plays out in the pharmaceutical and biotechnology industries. Industries innovate differently, thus conclusions about patents in general or about a specific industry do not always apply to a particular industry.[47] Empirical research has shown that pharmaceutical and biotechnology industries are underrepresented in doctrine of equivalent cases compared to the mechanical and electronics industries, accounting for only 9.2% of doctrine of equivalents cases compared to 11.5% of all patents.[48] Several theories attempt to explain this discrepancy. One conjecture is that the doctrine was designed for mechanical inventions and thus works less well for other industries.[49] A second hypothesis suggests that the information technology industry changes rapidly and thus its inventions are less well expressed in patent claims, making the doctrine of equivalents more important than in the life sciences industry where it is easier to express the scope of an invention in the patent claim.[50] Regardless, the success rate for plaintiffs using the doctrine of equivalents is consistent (and consistently low) across industries.[51]

However, patents remain a vital part of the pharmaceutical industry[52] and uncertainty in patent boundaries would surely make it difficult for firms to raise funds and develop products.[53] Moreover, if the theory that the doctrine was designed for mechanical inventions and thus works best in that industry is true, it follows that the doctrine would be less predictable and less well applied in the life sciences industries, leading to even more confusion and uncertainty. In addition, most pharmaceutical and biotechnology cases involve complex science, and many studies have shown that juries (and judges) struggle with

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note 43, at 1374.

46. Donald S. Chisum, *The Scope of Protection for Patents After the Supreme Court's Warner-Jenkinson Decision: The Fair Protection-Certainty Conundrum*, 14 SANTA CLARA COMPUTER & HIGH TECH. L.J. 1, 1, 62 (1998).

47. *E.g.*, Dan L. Burk & Mark A. Lemley, *Policy Levers in Patent Law*, 89 VA. L. REV. 1575 (2003).

48. Allison & Lemley, *supra* note 38, at 972-73.

49. *Id.* at 973.

50. Julie E. Cohen and Mark A. Lemley, *Patent Scope and Innovation in the Software Industry*, 89 CALIF. L. REV. 1, 45-47 (2001).

51. Allison & Lemley, *supra* note 38, at 973.

52. Natalie M. Derzko, *The Impact of Recent Reforms of the Hatch-Waxman Scheme on Orange Book Strategic Behavior and Pharmaceutical Innovation*, 45 IDEA 165 (2005) (explaining how FDA exclusivity periods are short enough that there is almost always a period of time when a drug is covered by a patent but not by market exclusivity).

53. *E.g.*, Henry Grabowski et al., *The Market for Follow-On Biologics: How Will it Evolve?*, 25 HEALTH AFF. 1291, 1300 (2006) ("[I]ncreased uncertainty and IP litigation in biotech also would have major negative-incentive effects on capital market decisions for developing private and public biotech firms with promising pipelines.").

scientific cases.[54]

Irrespective of the challenges inherent in the doctrine, it remains influential and popular. Over the past year, 190 district court cases cited the doctrine, and the Federal Circuit heard two doctrine of equivalents cases.[55]

II. BIOLOGICS AND FOLLOW-ON BIOLOGICS

Biologics are regulated under the Public Health and Service Act (PHSA).[56] A biologic, or "biological product" is defined to mean "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."[57] Biologics are complex proteins which are bigger, more intricate, and more poorly-understood than small molecule drugs.[58] Biologics can be extracted from animal cells or tissue that naturally produce the protein or scientists can genetically modify cells or tissue to create a system that produces larger quantities of the protein. Because of the potential to scale up production, most biologic proteins are produced using the latter technique.[59]

It is much more difficult to create (and to regulate) a "generic" biological product than a generic small molecule drug. Small molecule generics usually include an identical active ingredient which is chemically identical to the brand name drug's active ingredient, and which can be synthesized in a predictable and replicable process.[60] Small molecule drugs are also generally easy to characterize. Biologics, in contrast, cannot be synthesized chemically and are instead usually produced through a recombinant cell line.[61] Compounding these challenges, the details of the production process used by the pioneer company

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54. Alan Feigenbaum, *Special Juries: Deterring Spurious Medical Malpractice Litigation in State Courts*, 24 CARDOZO L. REV. 1361, 1389-96 (2003); Jody Weisberg Menon, *Adversarial Medical and Scientific Testimony and Lay Jurors: A Proposal for Medical Malpractice Reform*, 21 AM. J.L. & MED. 281, 281 (1995).

55. To get a rough estimate of the number of cases citing the doctrine of equivalents, I searched on Westlaw's ALLFEDS database for "doctrine of equivalents" and restricted to "year to date" (searching between 01/13/2011 and 01/13/2012).

56. 42 U.S.C. § 262(j) (2006).

57. 42 U.S.C. § 262(i)(1) (2006).

58. *See, e.g.*, Alan J. Morrison, *Biosimilars in the United States: A Brief Look at Where We Are and the Road Ahead*, 26 BIOTECHNOLOGY L. REP. 463, 465 (2007).

59. Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition*, B.C. INTELL. PROP. & TECH. F., 2009, at 6.

60. Jeanne Yang, *A Pathway to Follow-On Biologics*, 3 HASTINGS SCI. & TECH. L.J. 217, 221 (2011).

61. *Id.* Note this inability to synthesize the biologic only extends to protein drugs. Some nucleotide products can be synthesized chemically.

are protected by various intellectual property methods.[62] The production process is thus not fully controlled (or understood), and small differences in production process—or even production by the same process but in a different facility—can result in differences in the product, which can have adverse clinical consequences.[63] Moreover, it may not even be possible, given the current state of scientific knowledge, to determine whether two biologics are, in fact, identical.[64]

Because of the challenges in reproducing biologics and the lack of sensitive assays for differences,[65] the data requirements for comparing follow-on biologics to a reference product are likely to be considerably higher than the data requirements for generic companies comparing their small molecule drug to a reference product.[66] Small molecule drug manufacturers are usually required to conduct approximately 40 to 50 clinical tests, whereas follow-on biologic manufacturers in Europe (which has had follow-on biologic legislation

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62. Islah Ahmed et al., *Follow-on Biologics: Impact of Biologic Product Life Cycle and European Experience on the Regulatory Trajectory in the United States, Clinical Therapeutics* (forthcoming, 2012) (manuscript at 4) (on file with author),; *See also* U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ET AL., GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT (DRAFT GUIDANCE), 5-6 (February 2012) [hereinafter *Scientific Considerations*] ("[T]he manufacturer of a proposed [biosimilar] product will likely have . . . . . .no direct knowledge of the manufacturing process for the reference product.").

63. Paul J. Declerck, *Biotherapeutics in the Era of Biosimilars: What Really Matters is Patient Safety*, 30 DRUG SAFETY 1087, 1088 (2007) ("Small distinctions in the cell line, the manufacturing process or in any step from the cell line stage through to administration to the patient can make a major difference in adverse effects observed during treatment . . . . Therefore, unlike chemical pharmaceuticals, substitutions between biologics, including [follow-on biologics], can have clinical consequences and create health concerns for patients.").

64. Erika Lietzan & Emily Alexander, *Biosimilars: What US Regulators Might Learn From Others*, REG. AFF. PHARMA 18, 19 (2011) (Speakers at the FDA's comment session regarding implementation of the BPCIA "disagreed sharply over whether it is even possible for a biosimilar applicant to satisfy [the BPCIA's interchangeability] standard given the current state of science."); *see also* Ahmed, *supra* note 62 ("In theory you can develop technology sensitive enough to establish clinically relevant thresholds of heretogeneity such that Hatch-Waxman type structure could be applied. In practice, this is extremely challenging because it is difficult to establish a correlation between biophysical differences and clinical effects."); Derclerck, *supra* note 63, at 1089 ("As a consequence of the complexity of both the biotechnology product and the production process . . . and the limitation of sensitivity of analytical tools (i.e. the process determines the product), no solid scientific grounds exist to guarantee safe interchangeability between any biologics . . . obtained through different manufacturers.").

65. *See, e.g.*, Ahmed, *supra* note 62 ("For many structurally complex drugs, current technology is insufficient for establishing the identical nature of the active molecule in comparison to the approved reference.").

66. *See, e.g.*, 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, 624 (2011) ("[T]he burden of evidence for generic biologics applicants could be far higher than it is for generic drugs . . .").

since 2003) are required to conduct over 200 tests.[67] In addition, the plain language of the BPCIA seems to require much more data than the plain language of the Hatch-Waxman Act.[68] Moreover, the BPCIA empowers the FDA to request additional data beyond the statutory requirements, whereas the Hatch-Waxman Act explicitly does not allow this.[69]

Despite these difficulties, economic pressure to lower healthcare costs led governments worldwide to attempt to develop an abbreviated approval pathway for generics. Many countries, including Canada, Japan, Korea, and the European Union, have developed such pathways.[70] In the United States, various lobbying groups and members of Congress began to push for new legislation to create such a pathway.[71]

In 2009, Congress passed the Biologics Price Competition and Innovation Act (BPCIA),[72] a subtitle within the larger Patient Protection and Affordable Care Act. The statute defines follow-on biologic to mean "(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[73] The statute also describes the data requirements for a follow-on biologic application. An applicant must submit "analytical studies that demonstrate that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and animal studies and clinical studies that are "sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use . "[74] The applicant must also show that both products use "the same . . mechanisms of action" and that "the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product" and that the facility in which the follow-on biologic is produced "meets standards designed to assure that the

67. Ingrid Kaldre, *The Future of Generic Biologics: Should the United States 'Follow-On' the European Pathway?* 9 DUKE L. & TECH. REV. ¶14 (2008).

68. Stroud, *supra* note 66, at 625 ("[The follow-on biologics] standards outlined [in the BPCIA] will require additional studies showing that the physical chemical structures of the two biologics are highly similar.").

69. *Id.* at 627.

70. For a discussion of the differences in the regulatory schemes of the countries that have an abbreviated biologics pathway, see Noel Courage & Ainslie Parsons, *The Comparability Conundrum: Biosimilars in the United States, Europe and Canada*, 66 FOOD & DRUG L.J. 203 (2011).

71. For a description of the legislative history of the BPCIA, *see generally*, Krista Hessler Carver, Jeffrey Elikan & Erika Lietzan, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 FOOD & DRUG L.J. 671 (2010).

72. 42 U.S.C. § 262 (2012).

73. 42 U.S.C. § 262(i)(2) (2012).

74. 42 U.S.C. § 262(k)(2)(A)(i) (2012).

biological product continues to be safe, pure, and potent."[75]

The BPCIA also includes a provision for determining when a follow-on biologic is sufficiently similar to the reference product that it may be deemed "interchangeable" with the reference product and be substituted for the brand name drug by a pharmacist even if the physician did not prescribe the follow-on biologic.[76] The standard for "interchangeability" is a product that "(i) is biosimilar to the reference product; and (ii) can be expected to produce the same clinical results as the reference product in any given patient . . ."[77]

Unlike the Hatch-Waxman Act, the BPCIA does not include a 180-day exclusivity period for the first generic company to challenge a patent, or a 30-month stay when a brand name company sues.[78] In addition, the BPCIA includes an "anti-evergreening" provision: a list of improvements in a drug that do not qualify for an exclusivity period—an effort to reduce the strategic small improvements made by producers of small molecule drugs in an attempt to extend their market monopoly.[79] The anti-evergreening provision provides that the following improvements will not receive exclusivity: (i) "a supplement for the biological product that is the reference product" or an application filed by the sponsor of the original reference product for a change "that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength" or "a modification in the structure of the biological product that does not result in a change in safety, purity, or potency."[80] Further, the BPCIA gives brand-name companies twelve years of data exclusivity as compared to the Hatch-Waxman Act's five years of market exclusivity.[81]

The interpretation of many portions of the BPCIA has been left to FDA discretion.[82] The FDA must define "highly similar" and "interchangeable."[83] In addition, the FDA must determine what tests must be done and what data must be acquired in order to satisfy the similarity requirements.[84] The FDA has indicated that it will look at biologics on a case-by-case basis, rather than a one-size-fits-all approach. The FDA Commissioner, Dr. Margaret Hamburg, stated that "there will not be a 'one-size-fits-all' approach. There will, rather, be a science-driven, case-by-case decision-making process rooted in the

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75. *Id.*

76. 42 U.S.C. § 262(i)(3) (2012).

77. 42 U.S.C. § 262(k)(4) (2012).

78. Henry Grabowski, Genia Long & Richard Mortimer, *Implementation of the Biosimilar Pathway: Economic and Policy Issues*, 41 SETON HALL L. REV. 511, 515 (2011).

79. For a comprehensive discussion of evergreening, *see* ROBIN FELDMAN, RETHINKING PATENT LAW 170-77 (2012).

80. 42 U.S.C. § 262(k)(7)(C) (2012).

81. Patient Protection and Affordable Care Act, 124 Stat. 119 (2010).

82. 42 U.S.C. § 262(k)(8) (2012).

83. Courage & Parsons, *supra* note 70, at 215.

84. 75 Fed. Reg. 61498 (Oct. 5, 2010).

regulatory studies . "[85] Other FDA officials, including Dr. Janet Woodcock, Director for the Center for Drug Evaluation and Research, published an article in the New England Journal of Medicine stating that given "the complex nature of biologics, it's unlikely that a "one size fits all" systematic assessment of [follow-on biologicity] can be developed. Instead, FDA scientists will need to integrate various types of information to provide an overall assessment that a biologic is [follow-on biologic] to an approved reference product."[86]

On February 9, 2012, the FDA issued draft guidances for industry outlining how it will define "highly similar" and what studies it will require follow-on biologic companies to submit. The documents confirmed that the FDA will determine what evidence is required on a case-by-case basis, noting that the "type and amount of analyses and testing that will be sufficient to demonstrate [follow-on "biologicity"] will be determined on a product-specific basis."[87] In addition, the FDA indicated that its evaluation will not depend on any one piece of evidence, but it will instead "consider the *totality of the evidence* provided by a sponsor."[88]

The FDA explained that products must be "highly similar," citing the statutory language of "no clinically meaningful differences between [the products] in terms of safety, purity, and potency."[89] However, the document highlights certain areas where the FDA expects a follow-on biologic product might differ from the reference product. [90] The primary amino acid sequence must remain substantially the same, but "minor modifications such as N- or C-terminal truncations that will not affect safety and effectiveness may be justified . "[91] The choice of cell expression system is another area of possible difference, "because the type of expression system and host cell will significantly affect the types of process- and product-related substances and impurities . that may be present in the protein product."[92] Differences in post

85. Margaret A. Hamburg, Comm'r, Food & Drug Admin., Remarks at Generic Pharmaceutical. Ass'n Ann. Meeting (Feb. 18, 2010), available at http://www.fda.gov/NewsEvents/Speeches/ucm201833.htm.

86. Steven Kozlowski, Janet Woodcock, Karen Midthun & Rachel Behrman Sherman, *Developing the Nation's Biosimilars Program*, 365 NEW ENG. J. MED. 385, 386 (2011).

87. *Scientific Considerations*, *supra* note 62, at 8.

88. *Id.* at 2.

89. *Scientific Considerations*, *supra* note 62, at 3.

90. *See e.g.*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ET AL., GUIDANCE FOR INDUSTRY: BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 (DRAFT GUIDANCE), 4-5 (Feb. 2012) [hereinafter *Questions and Answers*] ("[D]ifferences between the formulation of a proposed product and the reference product may be acceptable . . .").

91. *Scientific Considerations*, *supra* note 62, at 9.

92. U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES ET AL., GUIDANCE FOR INDUSTRY: QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PROTEIN PRODUCT (DRAFT GUIDANCE), 9 (Feb. 2012) [hereinafter *Quality Considerations*].

translational modifications "might not preclude a finding of biosimilarity."[93] If "the manufacturing process produces different levels of impurities, the biosimilar can still be accepted by the FDA."[94] Differences "between the formulation of a proposed product and the reference product may be acceptable."[95] Finally, "some design differences in the delivery device or container closure system used with the proposed biosimilar product may be acceptable."[96]

The draft guidelines indicate that the FDA will require follow-on biologic companies to submit extensive studies demonstrating that their product is "highly similar" to the reference product if the follow-on biologic has any of the differences listed above. "The type, nature, and extent of any differences . . introduced by design or observed from comprehensive analytical characterization of multiple manufacturing lots, should be clearly described and discussed. . . . The potential effect of the differences on safety, purity, and potency should be addressed and supported by appropriate data."[97]

The FDA has not yet issued guidance on how it will determine interchangeability (which would allow pharmacists to substitute the follow-on biologic for the brand name drug). In its draft guidance, it notes that it has the power to make a determination of interchangeability, but "[a]t this time, it would be difficult as a scientific matter for a prospective [follow-on biologic] applicant to establish interchangeability . . "[98]

Although the FDA has not yet approved a drug under the follow-on biologic pathway, drugs that could be considered follow-on biologics have been approved in the United States though other pathways. Omnitrope™, a recombinant human-growth hormone (rhGH) produced by Sandoz was approved through the 505(b)(2) pathway.[99] The 505(b)(2) pathway is considered an "abbreviated" application pathway in the sense that applicants may rely on safety studies submitted by a pioneer drug manufacturers.[100] In its 505(b)(2) application, Omnitrope relied on studies done by Pfizer for their pioneer rhGH product Genotropin.[101] The FDA allowed Omnitrope to be approved through 505(b)(2), but emphasized that Omnitrope is a "relatively

93. *Scientific Considerations*, *supra* note 62, at 8.

94. *Quality Considerations*, *supra* note 92, at 12.

95. *Questions and Answers*, *supra* note 90, at 4.

96. *Id.* at 5.

97. *Quality Considerations*, *supra* note 92, at 8.

98. *Questions and Answers*, *supra* note 90, at 11.

99. Covington & Burling, FDA Approval of Sandoz's 505(b)(2) Application for a Follow-On Recombinant Human Growth Hormone Product, 1 (June 5, 2006), available at http://www.cov.com/files/Publication/8405cdb8-b5ca-4050-a2a7-84ea54b23aac/Presentation/PublicationAttachment/356e78e0-06fc-45e3-b0b8-9385b2b205b0/oid20985.pdf.

100. 21 C.F.R. § 314.3.

101. Covington & Burling, *supra* note 99.

simple recombinant protein [and] it is possible to determine that the end products of different manufacturing processes are highly similar "[102] Other biological drugs, including GlucaGen, Hylenex, and Fortical have also been approved through 505(b)(2) applications.[103] Shortly before the BPCIA was passed, Teva applied for a BLA for its product TevaGrastim (follow-on biologic to Amgen's Neupogen).[104]

III. WORK-AROUNDS AND INFRINGEMENT

Because no follow-on biologics have been approved under the BPCIA, courts have not yet addressed the question of infringement. However, the first biologics are starting to come off patent, meaning that they will go forward protected only by the weaker drug product, method, or product patents seen in the section on small-molecule drugs. This will spawn opportunities for follow-on biologic work-arounds which will, like their generic predecessors, struggle with maintaining sufficient similarity to the reference drug to satisfy the FDA while maintaining sufficient differences from the reference drug to avoid infringing by equivalents.[105] In this section, I make predictions about how

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102. Letter from Steven Galson, Dir., Center for Drug Evaluation and Res., to Kathleen Sanzo et al. 4 (May 30, 2005).

103. Courage & Parsons, *supra* note 70, at 213-14.

104. Press Release, Teva, Teva Announces the Submission Of A Biologics License Application (BLA) for XM02 for The Treatment Of Chemotherapy-Induced Neutropenia (Dec. 1, 2009); s*ee also* Courage & Parsons, *supra* note 70, at 214; Richard A. Epstein, *The Constitutional Protection of Trade Secrets and Patents Under the Biologics Price Competition and Innovation Act of 2009*, 66 FOOD & DRUG L.J. 285, 326 (2011). The FDA responded to Teva's BLA with a request for more information. *Id.* at n.190.

105. In the world of small molecule drugs, it is extremely common for brand name drugs to remain protected by peripheral patents and for generic companies to attempt to enter the market by working-around these patents. *See, e.g.*, Sanofi-Aventis v. Sandoz, Inc., 2009 WL 1741571 (D.N.J. 2009) (The plaintiff produces Eloxatin, an anti-cancer drug used in conjunction with chemotherapy to slow the growth of cancer cells in the body. The active ingredient is oxaliplatin, a chemical that can come in one of two orientations, called enantiomers, which are mirror images of each other. One enantiomer is toxic; therefore it must be separated out before the drug can be used. Plaintiff's patent claims "optically pure [oxaliplatin]," (meaning that the toxic enantiomer is completely separated out) purified using High Performance Liquid Chromatography (HPLC). The defendants both produce optically pure oxaliplatin using methods other than HPLC. The court found that because the generic products are not resolved using HPLC, they do not infringe by either literally or by equivalents); Astrazeneca Pharm. LP v. Mayne Pharma Inc., 2005 WL 2864666 (S.D.N.Y. 2005) (The plaintiff held a patent on Diprivan, a mixture of injectable propofol (an anesthetic) and disodium edetate (EDTA, an antimicrobial compound added to improve the shelf-life of the product). The generic company used a formulation that mixed injectable propofol with diethylenetriaminepentaacetate (DTPA), a compound similar to the EDTA used in the brand-name product. The court found that the generic did not literally infringe, but it did infringe by equivalents); Janssen Pharm. N.V. v. Eon Labs Mfg., Inc., 374 F. Supp. 2d 263 (E.D.N.Y. 2004) (The plaintiff produces brand-name Sporanox, an anti-fungal. The patent claims "Beads Having a Core Coated with an Antifungal and a Polymer" and further

follow-on biologic manufacturers and courts will handle this problem. I base my predictions off patent infringement cases for small molecule drugs, cases for biologics approved through BLAs or 505(b)(2)s, and the strategies used by follow-on biologic manufacturers who have had their products approved in other countries. I focus on how these cases will be treated under the doctrine of equivalents because the doctrine of equivalents represents the outer boundary of patent protection and thus is the most relevant to understanding how far follow-on biologics must stay from the reference drug's patent.

A. *What Will Follow-on Biologics Look Like?*

The types of work-arounds most commonly seen in small molecule drugs are changes to inactive ingredients, packaging, and chemical synthesis of the drug and stability agents.[106] Because the production process of biologics is much more complex, the approaches for biological work-arounds are likely to be somewhat different. Based on the predictions of several scientific scholars and industry experts,[107] I divide follow-on biologic work-arounds into the

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limits the claim to beads with a "polymer layer, characterized in that the core has a diameter of about 600 to about 700 um (25-30 mesh)." The defendant developed a bioequivalent formulation using a 20-25 mesh. The court held that defendant's product did not infringe either literally or by equivalents); Glaxo Wellcome, Inc. v. Pharmadyne Corp., 32 F. Supp. 2d 265 (D. Md. 1998) (The plaintiff makes Zantac, a medication used to treat heartburn and ulcers. Zantac is made from ranitidine hydrochloride combined with ethanol, an antimicrobial put into the solution to preserve shelf-life. The generic product combined ranitidine with propylene glycol, which is also an anti-microbial agent. The court found that the generic did not literally infringe, but did infringe by equivalents).

106. Janet Freilich, *The Paradox of Legal Equivalents and Scientific Equivalence: Reconciling Patent Law's Doctrine of Equivalents with the FDA's Bioequivalence Requirements*, 66 SMU L. REV. (forthcoming 2012).

107. My categories are based on categories listed in the following articles: Islah Ahmed et al, *Biosimilars: Impact of Biological Product Life Cycle and European Experience on the Regulatory Trajectory in the United States,* 34 CLINICAL THERAPEUTICS 400, 405 (2012). (Listing the following categories in Table 1: Cloning (coding gene, plasmid), Transformation/Transfection (host cell/method), Cell Culture (temperature/media/oscillation of cells), Purification (method of purification/removal of epitopes/formulation and packaging)); Wolfgang Jelkmann, *Recombinant EPO Production—Points the Nephrologist Should Know*, 22 NEPHROL. DIAL. TRANSPLANT. 2749, 2751 (2007). (Manufacturing steps influencing the product include: "Sequence of cDNA, type of vector/plasmid, promoter and other accessory DNA elements, type of host cell, technique of transfection, propagation of host cell clones, maintenance of production cultures, composition of culture medium, type of culture vials/bottles, type of fermenter/bioreactor, extraction and purification of recombinant product from culture medium, analysis of product, formulation."); Wolfgang Jelkmann, *Biosimilar Epoetins and Other "Follow-On" Biologics: Update on the European Experience*, 85 AMERICAN JOURNAL OF HEMATOLOGY 771, 771 (2010). ("The main factors influencing the composition of recombinant medicines are: (i) the plasmid (promoter, marker genes), (ii) the host cell (origin, species, clone), (iii) the culturing process (fermenter, culture media), (iv) the purification steps, (v) posttranslational modifications (oxidation, deamidation, addition of polymers), and (vi) the formulation and packaging."); Huub Schellekens, *Biosimilar Therapeutics—What Do We Need To Consider*, 2 NEUROLOGY

following categories for ease of discussion:

- Pre-transformation (changes in promoters, enhancers, termination sequences, selection markers, genetic sequences)
- Transformation (changes in cell lines, glycosylation patterns, transfection efficiency, transcription/translation efficiency)
- Cell culture (changes in temperatures, media, reactor turnover)
- Purification (changes in method of purification, removal of epitopes, degree of impurity)
- Formulation (changes in inactive ingredients such as buffers or stabilizing solutions)

Thus far, other countries have approved follow-on biologics with changes in several of these categories. The European Medicine Agency (EMA) has approved Zarzio and Filgrastim Hexal, two follow-on biologics of Neupogen, a drug used to stimulate white blood cell growth. Both Zarzio and Filgrastim Hexal are identical to Neupogen except that the buffer used in the follow-on biologics is glutamate while Neupogen uses acetate.[108] This is a formulation switch. The EMA has also approved Tevagrastim, Ratiograstim and Biograstim, also follow-on biologics to Neupogen.[109] These three follow-on biologics are identical to the reference product except for a slightly different pH and concentration of polysorbate 80 (used to stabilize solutions intended for parenteral administration). These are also formulation changes.

Both the EMA and the FDA have approved Valtropin, a recombinant human growth hormone. Valtropin was approved as an NDA in the United States[110] and as a follow-on biologic of Humatrope in Europe. Valtropin is produced in *S. cerevisiae* (yeast) whereas the reference product is produced in *E.coli.*[111] This is a cell line (or transformation) change.

The EMA approved Abseamed, Binocrit, Epoetin alpha Hexal, Retacrit, and Silapo, all follow-on biologics of Eprex, a recombinant epoetin which stimulates the production of red blood cells. They have different glycosylation levels and lower levels of neuraminic acid as compared to the reference

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DIALYSIS TRANSPLANTATION i27, i28 (2009). ("Changes may occur to the expression systems used for production, culture conditions (e.g. temperature and nutrients), purification and processing, formulation, storage and packaging . . . Structural differences between proteins may arise for a number of reasons, including oligomerization, modification of the primary protein sequence, glycosylation patterns or the conformational state . . ").

108. European Medicines Agency, European public assessment report (EPAR) for Zarzio (2009); European Medicines Agency, EPAR for Filgrastim Hexal (2009).

109. European Medicines Agency, EPAR for Biograstim (2008); European Medicines Agency, EPAR for Tevagrastim (2008); European Medicines Agency, EPAR for Ratiograstim (2008).

110. Center for Drug Evaluation and Research, Application Number: 21-905 Approval Letter (2007).

111. European Medicines Agency, EPAR for Valtropin (2012). // authorization removed

drug.[112] These are all transformation changes.

In addition, epoetin follow-on biologics approved in Korea (Eporon, Espogen, and Epokine) had a purity difference compared to the reference product.[113] The follow-on biologic products contained several different isoforms (a different form of the same protein) as compared to Eprex.[114]

Epoetin products (not follow-on biologics) have also been changed using PEGylation, a formulation change that involves attaching a polyethylene glycol (PEG) molecule to the protein to increase water solubility and thus stability and shelf-life.[115] Another formulation change used with epoetin involved changing the stabilizer from human serum albumin (HSA) to polysorbate 80.[116]

B. *How Will Each Category of Change Be Treated?*

In general, courts have been reluctant to hold that a change in a biotechnology product infringes under the doctrine of equivalents. This may be because courts struggle to understand the technology, or because scientists themselves struggle to understand how the mechanics of small changes affect the function, way, and result of biotechnologies to the same extent that they understand the function, way and result of small molecule drugs. In addition, there is very little precedent in this area, so courts may be reluctant to move ahead of the development of the case law and hold that a product does infringe by equivalents. Rather, courts prefer to leave the question to a jury by refusing to grant summary judgment to the patentee.[117]

The doctrine of equivalents will become an increasingly popular litigation strategy as follow-on biologics enter the market. Although the doctrine of equivalents has been litigated in non-drug biotechnology cases, these non-drug biotechnologies are not constrained by the FDA to closely resemble a patented product—the way that a follow-on biologic would be. Therefore scientists searching for a work-around have a larger number of variations to attempt, making it less likely that their product will infringe. Once follow-on biologics enter the market, the doctrine of equivalents is likely to become as highly used in the biotechnology sphere as it is in the small molecule drug sphere.

Follow-on biologic manufacturers, like small molecule drug

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112. European Medicines Agency, EPAR for Binocrit (2007).

113. *See* S. Park, K. Patel and J. Ko et al., *Analytical comparisons of erythropoietin products from Korea and Amgen's Epogen (epoetin alfa)*, 21 NEPHROL. DIAL. TRANSPLANT iv14 (2006).

114. Schellekens, *supra* note 107, at i29.

115. Amgen Inc. v. Hoffman-La Roche Ltd., 580 F.3d 1340, 1381 (Fed. Cir. 2009).

116. Michael Lissy et al., *Comparison of the Pharmacokinetic and Pharmacodynamic Profiles of One US-Marketed and Two European-Marketed Epoetin Alfas*, 11 DRUGS R. D. 61, 62 (2011).

117. Allison & Lemley, *supra* note 38, at 38 (remarking that in other contexts courts prefer to decide questions of infringement by equivalents on summary judgment).

manufacturers, will be forced to create a product that is similar enough to satisfy the FDA, but different enough to avoid infringing on the reference drug's patent. Of the possible categories of changes they can make—from pre-transformation changes to formulation changes—I will show that there will [be?] the broadest intellectual space for work-arounds far upstream from the final product, in the pre-transformation or transformation categories, or at the final stage, with formulation changes. This is because pre-transformation or transformation changes may not be as integral to the FDA's "highly similar" comparison, thus, there is more room to make changes as long as the end product is still "highly similar." Although formulation changes will certainly be part of the FDA's "highly similar" analysis, the statute explicitly allows changes in formulation, stating that although there can be "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product," changes in excipients are allowed.[118] Companies given more leeway by the FDA to make changes will be more likely to make changes further away from the boundaries of the patent, and thus less likely to infringe by equivalents.

Conversely, the middle stages of the production process—cell culture and purification steps—will be the most difficult for follow-on biologic companies to change while remaining "highly similar" and avoiding infringement by equivalents. Because the manufacturing process is an integral part of a biologic, and because small changes may have large—and poorly understood—effects, the FDA will likely govern all stages of the manufacturing process closely and require them to resemble the brand name company's manufacturing process. Thus, the space to stray from the process used by the innovator company will be very narrow, forcing follow-on biologics to stay closer to the patented formulation. Resultantly, they will be more likely to infringe.

Whether any particular work-around will be barred on the grounds of patent infringement will, of course, depend on the precise wording of the patent protecting the innovator product. However, there are trends in what types of work-arounds are more likely to allow generic drugs to avoid infringement;[119] therefore, it stands to reason that there would also be trends for follow-on biologics. My conclusions will be useful to follow-on biologic companies because they suggest fruitful directions for research, and will be useful for brand name companies because they suggest areas that should be accounted for when developing a patent portfolio around a product.

1. *Pre-transformation changes*

Follow-on biologic companies will likely be able to make pre-transformation changes from the reference product that will allow them to

118. 42 U.S.C. § 262(i)(2).

119. Freilich, *supra* note 106.

create a product that does not infringe the brand-name patent. Pre-transformation changes include changes to the coding nucleic acid sequence and the use of different promoters, enhancers, or termination sequences. It will be easier for follow-on biologic companies to make changes to promoters, enhancers, or termination sequences than to the portion of the nucleic acid sequence that codes for the drug.

Although the FDA will restrict the range of changes a follow-on biologic company will be able to make at the pre-transformation stage, it will not do so to the same extent as [it will to?] some of the downstream steps. Therefore, follow-on biologic companies will be able to make a wider range of changes and will be more likely to be able to innovate far enough away from the boundary of the patent to avoid infringement. The FDA's requirement for a "highly similar" product applies to the finished product, not the starting material.[120] The FDA has indicated in its draft guidance documents that "minor modifications such as N- or C- terminal truncations that will not affect safety and effectiveness may be justified."[121] The draft guidances do not mention how the FDA will treat other pre-transformation changes, such as different promoters or enhancers, but presumably the FDA would allow the changes as long as the final product remained highly similar to the reference product and the change did not introduce additional impurities.[122]

The courts have favored defendants in cases involving pre-transformation changes. Although there are no cases addressing follow-on biologics, there have been a significant number of cases exploring the outer boundaries of patent protection in the context of pre-transformation techniques used in biotechnology. This is because pre-transformation technologies have been used extensively in laboratories and in biologics research. Courts have been extremely reluctant to hold that a pre-transformation change infringes under the doctrine of equivalents. Courts will not grant summary judgment to a plaintiff moving for a decision on infringement by equivalents, and will often grant summary judgment to a defendant moving for a finding of no infringement as a matter of law. However, courts deal more favorably with changes to promoters, enhancers, or termination sequences than to changes in the portion of the genetic sequence that encodes the protein.

Because there are many cases dealing with pre-transformation changes, follow-on biologic applicants can look to this law to predict how courts will treat follow-on biologic litigation. Courts have struggled to determine when a change in the DNA or amino acid sequence is small enough to infringe by

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120. *See generally Scientific Considerations*, *supra* note 62; *Quality Considerations*, *supra* note 92.

121. *Scientific Considerations*, *supra* note 62, at 9.

122. *Quality Considerations*, *supra* note 92, at 13 (noting that the guidance mentions the possibility of such impurities, suggesting that "process-related impurities arising from cell substrates (e.g., host cell DNA, host cell proteins) . . . should be evaluated.").

equivalents.[123] The Federal Circuit has stated that "[t]he mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence."[124]

A recent case where the court acknowledged the difficulty of applying the doctrine of equivalents to a defendant who used a different generic sequence is *Regents of University of California v. Monsanto Co.*[125] In *Regents*, the plaintiff held a patent on the recombinant nucleotide sequence encoding bovine growth hormone (bGH). Monsanto used a slightly different DNA sequence to encode its version of bGH, which plaintiff argued infringed by equivalents.[126] The court struggled to define the 'function' of the biotechnology product. The court was unsure whether the function of recombinant DNA is to "require expression of the bGH protein" or whether its function is "merely to provide a blueprint for bGH."[127] Because the outcome of the case turns on the definition of function, the court denied the plaintiff's motion for summary judgment, holding that whether the products were equivalent was a matter of fact.[128]

The Federal Circuit struggled with the question of how to apply the doctrine of equivalents to a change in nucleic acid sequence in *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*[129] In *Boehringer*, both companies made a vaccine for Porcine Reproductive Respiratory Syndrome (PRRS). The genetic sequence of the vaccines differed by at least 73 nucleotides.[130] A jury found that the defendant did infringe by equivalents. The Federal Circuit upheld the jury's verdict holding that "[a] reasonable jury could easily . . conclude that the genetic differences between [the two vaccines] are insubstantial in the context of the claimed method."[131] Note that the patent does not actually claim the genetic sequence; it merely names the strain of virus used in the vaccine, which was the reason for the court's caution about context—the result could have been different if the patent had described the vaccine using a different method.

Although the Federal Circuit in *Boehringer* upheld a jury verdict of infringement, in another genetic sequence case, the Federal Circuit upheld a

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123. *See* JANICE M. MUELLER, PATENT LAW 352 (3d ed. 2009) (questioning whether a change in a single nucleotide would be infringing, and concluding that the answers are likely to be case-specific); D. Alan White, *supra* note 44, at 762-3 (noting that it will be extremely difficult to apply the doctrine of equivalents to small changes in generic sequences).

124. Boehringer Ingelheim Vetmedica, v. Schering-Plough, 320 F.3d 1339, 1353 (Fed. Cir. 2003).

125. Regents of University of California v. Monsanto Co., No. C 04-0634 PJH, 2005 WL 3454107 (N.D. Cal. Dec. 16, 2005).

126. *Id.* at *8.

127. *Id.*

128. *Id.*

129. 320 F.3d 1339. (Fed. Cir. 2003).

130. *Id.* at 1352.

131. *Id.*

jury verdict of non-infringement. In *Genentech, Inc. v. Wellcome Foundation Ltd*,[132] Genentech held patents covering the protein t-PA (tissue plasminogen activator) that dissolves stroke-causing fibrin clots and restores blood flow. The patent covered the DNA sequence, the expression vector containing the sequence, the cell culture capable of expressing t-PA using the vector, and the process for producing recombinant t-PA.[133] Defendants made FE1X, a protein variant of t-PA. FE1X lacks a structure of t-PA called the finger region and has a one amino acid substitution, which changes the glycosylation pattern.[134] After a jury trial returned a verdict of infringement by equivalents, the defendants asked the court to hold that FE1X could not infringe as a matter of law.

The court applied the function-way-result test but struggled to define the 'function' prong. While the trial court found that the function of t-PA was "dissolution of fibrin clots through the cleavage of plasminogen to plasmin," the Federal Circuit worried that if this was true: it "is difficult to imagine how any version of t-PA . . . would avoid infringement under the doctrine of equivalents because t-PA, or any operative variant, would by definition necessarily perform this function in the same general way with the same results."[135] Therefore the Federal Circuit defined the function of t-PA to be "catalyzing the conversion of plasminogen to plasmin, [and] bind[ing] to fibrin."[136] Based on this definition, the court held that FE1X did not function substantially the same way or achieve substantially the same results because the different structure of FE1X resulted in a significant change in binding efficiency and a roughly ten times increase in half-life.[137] Therefore the court held that there was no infringement as a matter of law.[138]

In a similar case, *Carnegie Mellon University v. Hoffman-LaRoche, Inc.*,[139] plaintiff had a patent on a "recombinant plasmid containing a cloned complete structural gene encoding DNA polymerase I."[140] The court construed the term "DNA polymerase I" to mean an enzyme that, among other things, had 3'-5' exonuclease activity.[141] Defendant's product, *Taq* polymerase,[142] does not

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132. Genentech Inc. v. Wellcome Found., 29 F.3d 1555 (Fed. Cir. 1994).

133. *Id.* at 1558.

134. *Id.* at 1559.

135. *Id.* at 1567 (internal quotation marks omitted).

136. *Id.*

137. *Id.* at 1569.

138. *Id.*

139. Carnegie Mellon Univ. v. Hoffman-LaRoche, Inc., 55 F. Supp. 2d 1024 (N.D. Cal. 1999).

140. *Id.* at 1028.

141. *Id.* at 1045.

142. *Taq* polymerase is named after the bacteria from which it was derived—*Thermus Aquaticus*.

have 3'-5' exonuclease activity.[143] Plaintiffs argued that *Taq* polymerase infringed by equivalents because DNA polymerase I's 3'-5' exonuclease activity includes a proofreading function, and *Taq* polymerase also performs a proofreading function.[144] The court, relying on *Genentech v. Wellcome*, found that *Taq* polymerase is missing the amino acids used for 3'-5' exonuclease activity and did not perform a proofreading function in the same way.[145] Thus, the defendant's product did not infringe by equivalents.

As demonstrated in the cases above, courts are unsure of how to treat changes in genetic sequence under the doctrine of equivalents. In general, changes in genetic sequence will likely run into the most trouble with the 'way' prong of the equivalents test. A change to the genetic sequence that will be more likely to produce a product that is "highly similar" to the reference drug will be less likely to change the way the protein interacts with its target. A change to the genetic sequence that changes the way that the protein interacts with its target will likely effect how the drug functions, and thus it will be harder for the drug to obtain FDA approval as a follow-on biologic.

However, depending on the brand name patent in question, follow-on biologic companies may not need to alter the genetic sequence that codes for their protein in order to make a pre-transformation change. They may also be able to use a different promoter or enhancer, or make some other modification to the pre-translational process. Courts have been very favorable to defendants in cases involving this sort of change.

In *Regents of University of California v. Dako North America, Inc.*,[146] plaintiff held a patent on a method of using complementary DNA segments to bind to DNA in a cell. Defendants had a similar binding system which used peptide nucleic acid (PNA) instead of DNA. PNA is a synthetic molecule similar to DNA except that it has a polyamide backbone and binds more tightly to complementary DNA than DNA or RNA would.[147] Plaintiffs argued that the PNA product infringed by equivalents and moved for summary judgment. The court found that the "function and result" prongs were the same as a matter of law, but could not find that they functioned the same *way* as a matter of law because PNA binds more selectively and effectively than DNA.[148] Thus, the two inventions were not equivalent as a matter of law.

In *Gen-Probe v. Vysis*,[149] Vysis held a patent on DNA probes that capture and amplify a DNA sequence. The court constructed "amplification" to mean

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143. *Id.* at 1045.

144. *Id.*

145. *Id.* at 1046-47.

146. Regents of Univ. of Cal. v. Dako N. Am., Inc., 615 F. Supp. 2d 1087 (N.D. Cal. 2009).

147. *Id.* at 1090.

148. *Id.* at 1095-98.

149. No. 99-CV-2667 H(AJB), 2002 WL 34413199 (S.D. Cal. 2002).

non-specific amplification.[150] Vysis used non-specific random hexamers to bind to all DNA in a sample and to amplify the entire sample. Gen-Probe used specific primers to bind to a pre-determined sequence, and amplify only that sequence.[151] A jury found that Gen-Probe did not infringe by equivalents, and Vysis asked for a judgment as a matter of law.[152] The court found that the jury was given evidence that Gen-Probe's system had a different function (using specific primers, rather than non-specific random hexamers), operated a different way (by using specific primers and promoters rather than non-specific primers and promoters), and had a different result (increasing the proportion of the target sequence compared to the overall pool of nucleic acid, rather than increasing the proportion of all nucleic acid).[153] Thus, the court did not overturn the jury verdict.

The sorts of changes demonstrated in these two cases could all be applied to some aspect of the pre-transformational process of producing a follow-on biologic. The FDA has been silent on this type of change, but it is unlikely to affect the final product; therefore generic companies will be able to make a wide range of changes. In addition, courts lean towards finding no infringement for pre-transformational changes.

Why are non-coding sequence types of pre-transformation changes easier to make? First, non-coding sequences may be changed while still producing an identical product,[154] meaning that they may be changed with less concern that the FDA will reject the product for lack of biosimilarity. This means that there is much wider room for change, and it follows that work-arounds for these sequences will fall further from the boundaries of the brand name company's patent than patent work-arounds in areas where deviation from the reference product is more closely regulated by the FDA.

Another advantage for follow-on biologic companies making changes at the pre-transformation stage is that this type of change has been the most heavily litigated to date. This is simply because pre-transformation technology was developed earlier and has been used for longer. The majority of the litigation does not concern biologic medicine used in humans, which is a relatively recent phenomenon, but rather biotechnology used in the lab, which traces its origins to the 1970s.[155] With a longer history comes more litigation.

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150. *Id.* at *11.

151. *Id.* at *13.

152. *Id.*

153. *Id.*

154. Note that while some pre-transformation changes, such as changes in nucleic acids, may result in a different product, they will not necessarily do so. A several base change in a DNA sequence may still produce the same amino acid sequence, resulting in an identical protein.

155. *See* Sally Smith Hughes, *Making Dollars out of DNA*, 1974-1980, 92 ISIS 541, 542 (2001) (describing how recombinant DNA revolutionized the biotechnology field. Recombinant DNA was also one of the first biotechnologies to be patented). For more

A high volume of litigation benefits follow-on biologic companies for several reasons. First, they will be better able to predict how courts will treat any particular change and how broadly courts will define the boundaries of a brand name patent. This predictability will allow them to design a work-around that they can be more confident will not infringe by equivalents. Moreover, if they engage in litigation, a greater number of precedential cases should allow the case to settle more quickly.[156] Finally, the greater volume of litigation and the longer history of how biotechnology works at a pre-transformation level will allow the litigants to provide more evidence to satisfy the 'function' and 'way' prongs of the test that courts have struggled with.[157] However, this longer history of litigation benefits brand name companies too. They can draft stronger patents based on how courts have treated earlier patents, and will also have a greater understanding of the technology and will be able to provide more evidence to the court. Nevertheless, pre-transformation changes will provide fruitful ground for follow-on biologic work-arounds.

2. *Transformation changes*

Transformation changes include use of different cell lines, different glycosylation patterns, and improvement in transfection efficiency. There is some overlap between the technologies placed in the transformation category and technologies placed in the pre-transformation category, and many of the

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information on the effect of the rDNA patent on biotechnology patenting practices *see* Janet Freilich, *A Nuisance Model for Patent Law*, U. ILL. J.L. TECH. & POL'Y 329, 363 (2011).

156. *See* Steven Shavell, FOUNDATIONS OF ECONOMIC ANALYSIS OF LAW 401 (2004) (demonstrating that parties are more likely to settle if their predictions of the outcome of the case are closer together).

157. This has traditionally been a problem in small molecule drug litigation. Courts want the plaintiff to produce specific evidence of how the defendant's product operates, and because many biological functions are poorly understood, this can be challenging for the plaintiff. *See, e.g.*, Cephalon v. Watson, 769 F. Supp. 2d 729 (D. Del. 2011) (Plaintiff produces Fentora, a product used to treat breakthrough pain in cancer. The drug consists of fentanyl buccal tablets given sublingually, which evolve gas by means of an effervescent reaction to increase the rate of absorption across the oral mucosa. The plaintiff produces the effervescent reaction using sodium bicarbonate. The plaintiff alleged that the defendant infringed because their generic tablets were "bioequivalent to Fentora" but did not provide any evidence of the nature of the chemical reaction occurring or conduct experiments to determine the rate and extent of absorption across the oral mucosa. The court scolded the plaintiff for lack of evidence and held that there was insufficient evidence to find infringement.); *see also* In re Omeprazole Patent Litig., 490 F. Supp. 2d 381 (S.D.N.Y. 2007) (Plaintiff produces Prilosec, used to treat ulcers. The active ingredient is omeprazole, a proton pump inhibitor which slows gastric acid secretion. The plaintiff's product contained an inert core coated with omeprazole, talc, hydroxypropyl methylcellulose, and several other coatings. The defendant's product contained different chemicals to stabilize the omeprazole. The court found that the plaintiff had not produced sufficient evidence to show that the chemicals in the defendants' product performed substantially the same function in substantially the same way to produce substantially the same result. The court therefore held that the defendants did not infringe).

points made about pre-transformation changes also apply to transformation changes. As with pre-transformation changes, courts have resolved cases in this category favorably for the defendant, therefore transformation changes will be a useful approach for follow-on biologic companies. However, as compared to pre-transformation changes, the FDA is likely to look more closely for similarity in transformation changes because differences in the transformation process can have a significant effect on the finished product. Production using a different cell line or a glycosylation change (glycosylation changes often come from using a different cell line) can affect the structure—and therefore function—of the protein.

European companies have successfully made follow-on biologics using transformation changes. Valtropin is grown in a different cell line than its reference product Humatrope™ (yeast versus *E. coli*) and has been approved as a follow-on biologic in Europe. It has also been approved in the United States through an NDA.[158] Valtropin is "analytically comparable to the marketed European reference product Humatrope."[159] Several follow-on biologics of the erythropoietin product Eprex have different glycosylation patterns but are nevertheless approved as follow-on biologics in Europe, and "[c]omparison of the purity and in-vivo bioactivity did not reveal any remarkable difference.[160]

The FDA is likely to approve follow-on biologics that have some transformation differences. Because there is a relatively large space between the reference drug and the limits of what would be considered follow-on biologic, it will be possible for generic companies to make a variety of changes, and thus to stay further from the reference product's patent and be less likely to infringe. In its draft guidelines, the FDA has indicated certain changes that may be acceptable as long as they do not produce clinically meaningful differences in safety, purity, and potency as compared to the reference product.[161] For example, the guidelines indicate that the FDA envisions some differences in the expression systems (cell lines) used to produce follow-on biologic products: "Differences between the chosen expression system of the proposed follow-on biologic product and that of the reference product should be carefully considered. . . "[162] The guidelines also indicate that the FDA envisions differences in amino acid modifications that can result from using different expression systems. The draft guidance states that "in general, proteins can differ [with respect to] . . modification to amino acids, such as sugar moieties

158. Center for Drug Evaluation and Research, Application Number: 21-905 Approval Letter (2007).

159. European Medicines Agency, European public assessment report (EPAR) for Valtropin (2012).

160. European Medicines Agency, European public assessment report (EPAR) for Silapo (2012)

161. *Scientific Considerations*, *supra* note 62, at 8.

162. *Quality Considerations*, *supra* note 92, at 9.

(glycosylation) or other side chains . . "[163] and that applicants should conduct tests to compare the post-translational modifications (such as glycosylation and phosphorylation) of the follow-on biologic and reference products.[164]

While the FDA is likely to allow follow-on biologics with transformation differences, its draft guidance documents caution that "[m]inimizing differences between the proposed and reference expression systems to the extent possible can enhance the likelihood of producing a highly similar protein product."[165] Thus, follow-on biologic companies must still take care to ensure that the changes they make do not have a substantial effect on the final product.

Because the FDA will allow follow-on biologic companies to make a range of transformation changes, follow-on biologic manufacturers will often be able to avoid infringing under the doctrine of equivalents. However, courts will probably find more infringement for transformation changes than for pre-transformation changes. This is because while the changes are still far back on the manufacturing chain and thus will likely be less scrutinized by the FDA, giving the follow-on biologic company greater latitude to make changes that take it outside the area the reference drug's patent claims, the FDA will still carefully scrutinize transformation changes. In certain cases, it is possible that a transformation change could cause the FDA to categorize a drug designed as a follow-on biologic to be a completely new drug and not allow it to use the abbreviated pathway outlined in the BPCIA.

Transformation changes have already been litigated in the context of biotechnology—though not quite to the same extent as pre-transformation changes—lending some predictability to how courts will treat them. Courts have found that using a different vector to transform a cell or using a different cell line does not infringe by equivalents.

In *Enzo Biochem, Inc. v. Calgene, Inc.*,[166] the court found that using a different transformation vector did not infringe under the doctrine of equivalents. Both parties in the case make genetically modified tomatoes. Calgene genetically modified the tomato using cDNA, whereas Enzo used an inverted gene.[167] Enzo argued that Calgene infringed under the doctrine of equivalents. The court found that cDNA and an inverted gene have the same effect (they shut off the function of the target gene) but that the method they use to do so is different.[168] The court held that Calgene did not infringe by equivalents.[169]

Courts have also found that using a different cell line does not infringe

163. *Scientific Considerations*, *supra* note 62, at 5.
164. *Id.* at 9.
165. *Quality Considerations*, *supra* note 92, at 10.
166. Enzo Biochem, Inc. v. Calgene, Inc., 14 F. Supp. 2d 536 (D. Del. 1998).
167. *Id.* at 560.
168. *Id.*
169. *Id.*

under the doctrine of equivalents. *Enzo v. Calgene* deals briefly with the question, pointing out that Enzo uses a prokaryote cell whereas Calgene uses a eukaryotic cell and concluding that this difference in cell types was not insubstantial.[170] *Carnegie-Mellon Univ. v. Hoffman-La Roche Inc.*[171] deals with the question in greater detail. In *Carnegie-Mellon*, the plaintiff held a patent on "the recombinant plasmid containing a DNA coding sequence for the expression of DNA polymerase activity . . wherein the bacterial host system and the bacterial source are each E. coli."[172] Hoffman-La Roche makes a recombinant plasmid that causes cells to express *Taq* DNA polymerase, which is derived not from *E. coli* but from *Thermus aquaticus*, a different type of cell.[173] Because *Taq* polymerase is not from *E. coli*, it does not literally infringe on the patent, but plaintiff argued that it infringed by equivalents. The court held that there was no infringement by equivalents.[174]

As these cases show, the trend in transformation change cases is to find that the defendant's product does not infringe by equivalents. In addition, these cases all involved relatively well understood technologies, meaning that the plaintiff will be more likely to be able to prove its case. This suggests that changing the transformation vector or cell line is a sufficient change that such a product would not infringe by equivalents on a patent that included a cell type as a limitation.[175] However, all infringement cases are fact-dependent, and it is easy to imagine a scenario where a closely related cell line, or a vector with an insubstantial difference, was used in the defendant's product, in which case that product might infringe by equivalents. Nevertheless, transformation differences are overall a good target for follow-on biologic companies seeking to make a change that is does not infringe.

3. *Cell culture changes*

Cell culture is the process of growing the cells that produce the biologic drug. Depending on the drug, it may not have a cell culture step (if it is made synthetically or is harvested from tissue) but most biologics on the market are produced through cell culture. Changes to cell culture may include growing cells at a different temperature, in different media, or increasing the reactor turnover. Changes in cell culture can be closely related to changes in purity, because the method of cell culture can often affect the purity of the resulting

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170. *Id.*

171. Carnegie-Mellon Univ. v. Hoffman-La Roche Inc., 541 F.3d 1115 (Fed. Cir. 2008).

172. *Id.* at 1128.

173. *Id.* at 1119.

174. *Id* at 1129.

175. Though of course the outcome is fact-dependent. It is easy to imagine a scenario where a closely related cell line was used for the defendant's product, in which case that product might infringe by equivalents.

product. It is likely that it will be very difficult for follow-on biologic companies to make changes in cell culture large enough to avoid infringing without running afoul of the FDA's "highly similar" regulations.

Unlike the unwillingness to find infringement by equivalents seen in pre-transformation and transformation cases, the court in the leading (and only) cell culture change case upheld a jury verdict of infringement by equivalents. In *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*,[176] the plaintiff held a patent on growing and isolating a pig virus using a process of incubating monkey cells containing the virus until a cytopathic effect (a visible change in the monkey cells due to viral infection) was observed.[177] The defendant also grew the pig virus in monkey cells, but instead of incubating until a cytopathic effect was observed, defendant incubated for a specified time period.[178] The jury was presented with evidence that the defendant was aware of the time required to achieve a cytopathic effect, and in fact may have based their time measurements off that period, and that the incubation period was similar to plaintiff's incubation period. The jury found that Schering-Plough's process did infringe.[179] On appeal for judgment as a matter of law, the Federal Circuit held that the jury was presented with evidence that "Schering's practice of incubating the viral culture for a defined period of time performs the same function, in the same way, with the same result as incubating the viral culture until a defined degree of [cytopathic effect] is observed," and did not overturn the verdict.[180]

One lesson from this case is the danger of encouraging follow-on biologic companies to change a drug just enough to avoid infringement. Although the court in this case came to the right conclusion, it is easy to imagine a follow-on biologic company using Schering-Plough's strategy. While a cleverer change might have avoided infringement, it could also place patients in danger. Boehringer's process for determining the incubation period relied on examining the cells to determine that enough viruses had grown. Schering-Plough's process for determining the incubation period involved using a proxy. Proxies are often less accurate than the measures they are based on. Thus there might be a small difference in the amount of virus produced in each batch. While most pigs would probably be effectively vaccinated, perhaps a few pigs would not be. Schering-Plough's maneuvering to get around the patent introduced unnecessary risk to the patient. This is not an outcome courts should encourage.[181]

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176. Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp., 320 F. 3d 1339 (Fed. Cir. 2003).

177. *Id.* at 1343.

178. *Id.* at 1344.

179. *Id.* at 1350.

180. *Id.* at 1353.

181. However, courts should also not be responsible for determining issues of safety, which are the responsibility of the FDA. Courts are notoriously poor at resolving questions

Besides the court's unfavorable treatment of the above cell culture case, a further reason to believe that cell culture will be a difficult place for follow-on biologic companies to make changes is because of FDA scrutiny. Process is a crucial part of ensuring that follow-on biologics are similar to the reference drug. Unlike small molecule drugs, where identical drugs can be made by very different processes, small changes in the biologic manufacturing process can produce disproportionately sized changes in the final product.[182] Because of the

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of science, making it difficult for them to adequately determine whether a product is safe or not. For discussion of courts' difficulty with scientific questions *see, e.g.*, Peter Lee, *Patent Law and the Two Cultures*, 120 YALE L.J. 2, 7 (2010); *see also* Arti K. Rai, *Engaging Facts and Policy: A Multi-Institutional Approach to Patent System Reform*, 103 COLUM. L. REV. 1035, 1040 (2003) ("Generalist trial judges, and the juries empanelled by trial judges, may be overwhelmed by the technology involved in patent cases."); Dan L. Burk & Mark A. Lemley, *Is Patent Law Technology-Specific?* 17 BERKELEY TECH. L.J. 1155, 1196 (2002) ("[J]udges are at a rather serious disadvantage in trying to put themselves in the shoes of an ordinarily skilled scientist."); Kimberly A. Moore, *Are District Court Judges Equipped to Resolve Patent Cases*, 15 HARV. J.L. & TECH. 1, 38 (2002) (concluding that "judges are not, at present, capable of resolving these [scientific patent] issues with sufficient accuracy"). Furthermore, judges themselves do not like scientifically complex cases. In the wake of *Daubert*, Judge Kozinski wrote that judges now face "a far more complex and daunting task in a post-*Daubert* world than before" (because judges are now responsible for claim construction). Daubert v. Merrell Dow Pharms., Inc., 43 F.3d 1311, 1315 (9th Cir. 1995). In a judicial panel discussion on science and law, the Honorable Alfred V. Covello stated, "I don't see how you could try a patent matter to a jury. Goodness, I've gotten involved in a few of those things. It's like somebody hit you between your eyes with a four-by-four." Judicial Panel Discussion on Science and the Law, 25 CONN. L. REV. 1127, 1145 (1993). Judge William Schwarzer wrote that science and technology issues "share one characteristic: They challenge the ability of judges and juries to comprehend the issues—and the evidence—and to deal with them in informed and effective ways." William W. Schwarzer, INTRODUCTION TO FED. JUD. CTR., REFERENCE MANUAL ON SCI. EVIDENCE 1, 1 (1st ed. 1994). The Supreme Court agreed, writing that "patent litigation can present issues so complex that legal minds, without appropriate grounding in science and technology, may have difficulty in reaching decision." Blonder-Tongue Labs., Inc. v. Univ. of Ill. Found., 402 U.S. 313, 331 (1971). Justice Scalia famously dismissed his understanding of scientific issues by quipping, "I told you before I'm not a scientist. (Laughter.) That's why I don't want to deal with global warming, to tell you the truth." Transcript of Oral Argument at 8, Massachusetts v. EPA, 127 S. Ct. 1438 (2007) (No. 05-1120).

182. Grabowski, *supra* note 78, at 515. Note that making changes production process is a very effective way for small molecule drugs to work-around a patent. *See, e.g.*, Sanofi-Aventis U.S. LLC v. Sandoz, Inc., 2009 WL 1741571 (D.N.J. 2009), *vacated*, 345 Fed. App'x. 594 (Fed. Cir. 2009) (plaintiff's patent covered a method of using High Performance Liquid Chromatography (HPLC) to purify their product. Both defendants found ways to purify the drug using other methods and the court found that they did not infringe.); SmithKline Beecham v. Apotex, 2005 WL 941671, *2 (E.D. Pa. 2005) (The plaintiff's product is Paxil, a blockbuster anti-depression drug. The plaintiff's conducted experiments with paroxetine, the active ingredient in Paxil, to "identify processes suitable for industrial scale production of paroxetine." They settled on a process that involved reacting an arecoline compound with a grignard reagent. This process could only be conducted in a non-ether solvent. The defendants created a synthesis process that works in an either solvent, which plaintiff's does not. Based on this, the court found that the defendants' process did not infringe.).

importance of process in the creation of a follow-on biologic product and because there are safety concerns attendant on a change in process, it is unlikely that the FDA will allow follow-on biologic manufacturers to make large changes in the cell culture process. Thus, it is unlikely that the follow-on biologic manufacturers will be able to make changes significant enough to avoid infringing.

4. *Purification changes*

It will be difficult for follow-on biologic companies to make purification changes in order to avoid infringing. Purification is part of the process of making the biologic, and, as with cell culture, small changes in the purification process could result in major changes to the safety of the drug.[183] Thus, it will be an area watched closely by the FDA, and the scope of changes follow-on biologic companies will be allowed to make will likely be narrow. The statute itself references purity, requiring that there be "no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product."[184]

There are two types of purity changes that follow-on biologic companies can make. They can make changes in the *level* of purity or they can make changes in the purification *process*. Because of the statutory requirement that there be "no clinically meaningful differences in terms of the . . purity"[185] of the product, follow-on biologic companies are unlikely to be able to make changes in the level purity that escape infringement by equivalents.

There are no cases involving the doctrine of equivalents and a level of purity change in a biologic, however there are several such cases involving generic small molecule drugs. The courts in the small molecule drug cases always found that the drug infringed.[186] This trend is likely to extend to follow-

183. Grabowski, *supra* note 78, at 516.

184. 42 U.S.C. § 262(i)(2)(B) (2006).

185. Id.

186. Pozen Inc. v. Par, Pharma., Inc., 800 F. Supp. 2d 789, 809 (E.D. Tex. 2011); Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 2006 WL 1582412, *5 (E.D. Va. 2006). In *Pozen*, the plaintiff produced Treximet, a painkiller used to treat migraines. Treximet combines two active ingredients, sumatriptan and naproxen, in two layers. It is a multilayer tablet protected by a patent which claims "substantially all of said triptan is in a first layer . . . and substantially all of said naproxen is in a second, separate layer." During claim construction, the court defined "substantially all" to mean "at least 90%." Defendants Par and Dr. Reddy's Laboratories each created an ANDA product that did not literally infringe. Par's product contained 85% of the naproxen in the first layer and 100% of the sumatriptan and 15% of the naproxen in the second layer. Dr. Reddy's product contained 85% of the sumatriptan in the first layer and 100% of the naproxen and 15% of the sumatriptan in the second layer. The court found that the products infringed by equivalents. In *Aventis*, the plaintiff's product is Altace, a medication made of the compound ramipril and used to treat high blood pressure. Plaintiff's patent covers ramipril "substantially free of other isomers." The defendant's generic product was made of ramipril containing between 0.06% and 0.5%

on biologics. A purity level change that receives FDA approval will not change the *function* of the drug because the active ingredient and bioavailability are the same. It will not change the *way* a drug functions because the active ingredient and bioavailability are again the same. It will not change the *result* because the active ingredient and bioavailability are the same. Therefore a follow-on biologic with a purity level change small enough that it is still approved as a follow-on biologic should always infringe by equivalents.

The second type of purity change a follow-on biologic company can make is in the purification *process*. These changes will be more likely to succeed in getting FDA approval and avoiding infringement. The FDA will still closely monitor the range of changes allowed relative to the brand name product, but it may be possible for a generic company to design a process that purifies a different *way*. There is only one case involving the doctrine of equivalents and a purification process change in biotechnology. In *Genentech, Inc. v. Boehringer*[187] the plaintiff patented a process for purifying proteins which included the step of "removing high molecular weight impurities using a molecular sieve or high speed centrifugation techniques."[188] The court construed 'molecule sieve' to mean gel permeation chromatography or gel filtration.[189] The defendant used a depth filter, not a gel, to remove high molecule weight impurities, so it did not literally infringe. Genentech argued that the depth filter is equivalent to high speed centrifugation since both have the same function—removing high molecular weight impurities from a solution.[190] The court disagreed. It found that centrifugation and filtration operate in different ways, the former by spinning a solution, and the latter by pouring a solution through a membrane. In addition, centrifugation separates particles by weight and solubility, whereas filtration separates particles by size.[191] Therefore Boehringer did not infringe by equivalents.[192]

Genentech is an example of a change in purification *process*. As the case demonstrates, it should be possible for follow-on biologic companies to make a change in process that does not infringe by equivalents. However, the results of small molecule drug cases suggest that it will not be possible to make a change in purity level that does not infringe by equivalents. Thus, brand name companies should patent their products by degree of purity, rather than by purification process (or ideally, by both). Follow-on biologic companies should seek to create work-arounds by inventing different methods of purification, rather than by changing the degree of purity.

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by weight of isomer-1. The court held that the defendant's product infringed.

187. Genentech, Inc. v. Boehringer Mannheim GmbH, 47 F. Supp. 2d 91 (D. Mass. 1999).

188. *Id.* at 116.

189. *Id.*

190. *Id.* at 117.

191. *Id.* at 116.

192. *Id.* at 120.

5. *Formulation changes*

Formulation changes involve changing inactive ingredients. Formulation changes will likely be some of the easiest changes for follow-on biologic companies to make. In general, changes in the formulations of small molecule drugs did not infringe by equivalents. In over 80% of cases, generic manufacturers that created work-arounds involving formulation changes did not infringe by equivalents.[193] The BPCIA gives follow-on biologic companies latitude to make formulation changes by explicitly allowing changes in inactive ingredients: "the biological product [must be] highly similar to the reference product *notwithstanding minor differences in clinically inactive components*."[194] It remains to be seen whether "minor differences" will allow manufacturers to make changes wide enough to avoid the patent infringement, but based on the experience of generic manufacturers it seems likely.

The experience of generic drug manufacturers is not completely analogous to biologics. Most formulation changes made in generic drugs involved incorporating the active ingredient into pills that can be taken orally while most biologics are given by injection, and cannot be given orally (yet). However,

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193. In 80% of cases, generic drugs involving a formulation work-around did not infringe. *Acorda* Therapeutics Inc. v. Apotex, Inc., 2011 WL 4074116 (D.N.J. 2011) (brand name drug: tizanidine on beads; generic drug: tizanidine granulation; court found no infringement); Cephalon, Inc. v. Watson, Pharm., Inc., 769 F. Supp. 2d 729 (D. Del. 2011) (brand name drug: sodium bicarbonate; generic drug: potassium bicarbonate; court found no infringement); Elan Corp. v. Andrx, Pharm., Inc., 2008 WL 4709251 (S.D. Fla 2008) (brand name drug: multi-particulate pellet form surrounded by multi-layer membrane; generic drug: pellet that does not dissolve completely during use, is not completely spherical and is not completely enclosed by membrane; court found infringement by equivalents); In re Omeprazole Patent Litig., 490 F. Supp. 2d 381 (S.D.N.Y. 2007) (brand name drug: talc and hydroxypropylmethylcellulose to stabilize core; generic drugs: other chemicals used to stabilize core; court found no infringement); Ranbaxy Lab. Ltd. v. Abbott, Lab., 2005 WL 3050608 (N.D. Ill. 2005) (brand name drug: drug mixed with "a pharmaceutically acceptable polymer;" generic drug: drug mixed with glycerin monostearate; court found infringement by equivalents); Janssen Pharm. N.V. v. Eon Laboratories, Lab. Mfg., 374 F. Supp. 2d 263 (E.D.N.Y. 2004) (brand name drug: beads with diameter of 600-700um; generic drug: beads with diameter of 700-800um; court found no infringement); Bristol-Myers Squibb Co. v. Andrx, Pharm., 343 F. Supp. 2d 1124 (S.D. Fla. 2004) (brand name drug: pregelatinized starch; generic drug: microcrystalline cellulose; court found no infringement); Bristol-Myers Squibb Co. v. Teva, Pharm. USA, Inc., 288 F. Supp.2d 562 (S.D.N.Y. 2003) (brand name drug: lubricant selected from stearyl fumarate or hydrogenated vegetable oil; generic drug: lubricants sodium lauryl sulfate and glyceryl behenate; court found no infringement); Biovail Corp. Int'l v. Andrx, Pharm., Inc., 158 F. Supp. 2d 1318 (S.D. Fla. 2000) (brand name drug: drug in admixture with wetting agent; generic drug: drug over core of sucrose and starch; court found no infringement); Upjohn Co. v. Mova Pharm. Corp., 31 F. Supp. 2d 211 (D.P.R. 1998) (brand name drug: spray-dried lactose making up 70% of composition; brand name drug: spray-dried lactose making up 49% of composition; court found no infringement); A.H. Robins Co. v. Erbamont, Inc., 1991 WL 229150 (S.D. Ohio 1991), *vacated* (brand name drug: hydrophilic surfactant external to microcapsule; generic drug: myristic acid in shell wall of microcapsule; court found no infringement).

194. 42 U.S.C. § 262(k)(2)(A)(i)(I)(aa) (2012) (emphasis added).

most biologics contain excipients dissolved in solution with the active ingredient; therefore, excipient changes in generic small molecule drugs are still relevant.

Biologics manufacturers in Europe have made changes to excipients. Filgrastim Hexal uses glutamate as its buffer, whereas the reference product, Neupogen, uses acetate.[195] The EMEA determined that the two buffer components were equally effective in maintaining the stability of the active ingredient.[196] The manufacturers of Eprex, an epoetin compound, originally used human serum albumin (HSA) as a stabilizer. They later switched to glycine and polysorbate 80, a formulation change (though Eprex is a pioneer drug, not a follow-on biologic).[197]

Only one U.S. court case has dealt with the doctrine of equivalents in the context of formulation changes in biologics. While the case does not give a definitive holding, it gives a hint at how courts will treat formulation changes. In *Amgen v. Hoffman-La Roche*,[198] the Federal Circuit addressed whether a change in Pegylation infringed by equivalents. Pegylation is the process of adding a polyethylene glycol (PEG) chain to a drug, which improves its water solubility and circulation time. Amgen held a patent claiming "a pharmaceutical composition comprising an effective amount of a glycoprotein product effective for erythropoietin therapy. "[199] Roche produces Pegylated erythropoietin. At trial, a jury found that Roche's product infringed by equivalents and Roche appealed for a judgment as a matter of law.[200] Amgen argued that it had presented evidence that Pegylation was equivalent to a composition "effective for erythropoietin therapy" because both compounds had the same function (to stimulate the maturation of bone marrow cells into red blood cells), way (by binding to an erythropoietin receptor) and result (making more blood cells).[201] The District Court found that Amgen's testimony was given as part of its literal infringement case, not as particularized testimony concerning the doctrine of equivalents, which is required, therefore the jury heard no evidence on the doctrine of equivalents, and so the jury verdict should be overturned. The Federal Circuit agreed.[202]

With little guidance from biologics cases, my predictions on how patent law will interact with formulation changes in follow-on biologics are derived

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195. European Medicine Agency Evaluation of Medicines for Human Use. Assessment Report for Filgrastim Hexal, 7, available at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Public_assessment_report/human/000918/WC500022471.pdf (last visited Dec. 12, 2012).

196. *Id.*

197. Schellekens, *supra* note 107, at i.30.

198. Amgen Inc. v. F. Hoffmann-La Roche Ltd., 580 F.3d 1340 (Fed. Cir. 2009).

199. *Id.* at 1380.

200. *Id.* at 1382.

201. *Id.* at 1381.

202. *Id.* at 1382.

from cases on small molecule drugs. As mentioned, many formulation changes made in small molecule drugs cannot be applied to biologics because the changes were to oral formulations, whereas most biologics are injected. This means that it will be more difficult for follow-on biologic manufacturers to make formulation changes that do not infringe by equivalents simply because there is a lower number of acceptable changes open to them, because biologics are offered in fewer types of dosage forms.

Furthermore, follow-on biologic manufacturers will have to focus on making changes that do not have a substantially similar function, way, or result on an element-by-element basis.[203] This means that the specific excipient that is switched will have to perform a different function, do so a different way, or achieve a different result. Courts also appear to be looking for true innovation, rather than mere copying. Courts in small molecule drug cases have shown that they have little patience for copies that generic companies tried to disguise as substantial changes.[204]

In addition, courts look for detailed evidence of how the excipient functions. In small molecule drug cases, courts have refused to find infringement because the plaintiff did not provide sufficient evidence of how the inactive ingredient performed the particular function.[205] It is possible that follow-on biologic companies will have an advantage when it comes to this information requirement because of the BPCIA's heightened data requirements for biologics. Data submitted to the FDA is not automatically evidence of legal equivalence, but the individual studies can be used to support an argument of equivalence (as long as the studies directly compare the drugs).[206]

In the process of completing the abbreviated BLA, follow-on biologic companies will have to provide evidence that "the biological product and

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203. *See* Acorda v. Apotex, 2011 WL 4074116 (D.N.J. 2011).

204. *See, e.g.*, Elan v. Andrx, 2008 WL 4709251 (S.D. Fla. 2008). In *Elan*, the plaintiff's product is Naprelan, a controlled release formulation of naproxen sodium, which is a pain reliever. Elan's patent claims naproxen in a multi-particulate pellet form, which creates the controlled release layer. Each pellet has a core of naproxen surrounded by a multi-layer membrane. The defendant claimed its product is different from the plaintiff's because (1) it is not a multi-particulate form because it disintegrates partially; (2) it is not a pellet because it is not completely spherical; and (3) it does not have a multi-layer membrane surrounding a core because its multi-layer membrane coating does not "completely enclose" the core. The court begins its analysis by noting that once scientists at Andrx decided to create generic naproxen sodium, they obtained a copy of Elan's patent to study. They tried various methods of mixing together ingredients until they settled on a formulation, which they felt was sufficiently different from Naprelan. The court was very skeptical of Andrx's changes, finding that all aspects of the generic drug performed substantially the same function in substantially the same way to obtain substantially the same result, and thus infringed under the doctrine of equivalents.

205. *See, e.g.*, In re Omeprazole Patent Litigation, 490 F. Supp. 2d 381 (S.D.N.Y. 2007); Cephalon v. Watson, 769 F. Supp. 2d 729 (D. Del. 2011).

206. *See* Adams Respiratory Therapeutics, Inc. v. Perrigo Co., 616 F.3d 1283, 1287-89 (Fed. Cir. 2010).

reference product utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed. . .but only to the extent the mechanism or mechanisms of action are known for the reference product."[207] This requirement is addressed to the active ingredient, not the excipient, but it seems likely the company will also need to understand how the excipients interact with the drug as compared to the reference drug's excipients. The FDA's draft guidelines also recommend that applicants assess "excipients and any formulation effect on purity, product- and process-related impurities, and stability."[208] This evidence will be helpful for proving their case in court.

Overall, formulation changes are a good target for follow-on biologic companies. It may be a less fruitful path for follow-on biologics relative to generics, because there are fewer dosage forms and thus fewer possible changes to make. However, the BPCIA's explicit allowance of excipient changes suggests the FDA will allow follow-on biologic companies to make a reasonably wide range of excipient substitutions, giving them more ground to avoid infringing by equivalents. Moreover, if the follow-on biologic companies are able to make a substantial change, the heightened data requirements means that they will likely have better data to use to prove that their change is substantial.

6. *Packaging changes*

Packaging changes involve changing the external container that holds the biological product. Packaging can be a very important part of a biologic because it can affect the stability of a product (for example, packaging may be required to keep out heat, light, or moisture) or improve ease of delivery. There are no packaging cases involving biologics. Therefore, my predictions in this section are based on packaging cases involving small molecule drugs. Although packaging biologics presents different concerns from packaging small molecule drugs, the way that the courts address the problem is likely to be similar.

The FDA has indicated a willingness to approve follow-on biologics that have different packaging from the reference product. In its draft guidance, the FDA stated that "some design differences in the delivery device or container closure system used with the proposed follow-on biologic product may be acceptable."[209] The FDA gave the example of auto-injectors, a syringe that already contains a pre-determined amount of a drug, which cuts out the step of filling the needle before injection. The draft guidance states that it "may be possible, for example, for an applicant to obtain licensure of a proposed biosimilar product in a pre-filled syringe or in an auto-injector device. .even if

207. 42 U.S.C. § 262 (k)(2)(A)(i)(II).

208. *Scientific Considerations*, *supra* note 62, at 9.

209. *Questions and Answers*, *supra* note 90, at 5.

the reference product is licensed in a vial presentation."[210] However, the FDA emphasizes that it is still necessary for a follow-on biologic with a packaging change to meet "the statutory standard for biosimilarity."[211]

Several cases involving the packaging of small molecule drugs and the doctrine of equivalents have been litigated.[212] The results were mixed, with half the courts finding infringement. The difference lies in the 'way' prong of the doctrine of equivalents test (although the courts do not all use this language). In *Abbott Laboratories v. Baxter Healthcare Corp*, the plaintiff solved the problem of degradation by mixing its drug with water.[213] The defendant solved the problem of degradation by creating a package lining that physically blocked the drug from coming into contact with the walls of the container, the source of the degrading chemical.[214] The court found that there was no infringement because the products prevented degradation in a different *way*.[215] Conversely, in *Mead Johnson & Co. v. Barr Laboratories, Inc.*, the plaintiff patented a method of scoring a pill in order to help a patient divide it into sections.[216] The plaintiff's product had opposing score notches, whereas the defendant's product had transverse score notches. The court found that there was infringement, noting that both products facilitated tablet breakage the same *way*—by directing pressure applied by the patient to achieve a more uniform fracturing.[217]

Packaging is a promising area for follow-on biologic companies because it appears both that the doctrine of equivalents will not bar all packaging changes and that the FDA will allow a relatively broad range of packaging changes. The comparison of *Abbott Laboratories v. Baxter Healthcare Corp.* and *Mead Johnson & Co. v. Barr Laboratories, Inc.* indicates that courts are willing to find that a packaging change does not infringe by equivalents as long as they are convinced that the containers function in different ways. Follow-on biologic companies could overcome the doctrine of equivalents by changing the packaging of their products if that packaging improved the stability of the product or ease of delivery in a different way. The FDA's draft guidance indicates that the FDA will allow packaging changes as long as the products

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210. *Id.*

211. *Id.*

212. Abbott Laboratories v. Baxter Healthcare Corp, 660 F. Supp. 2d 882 (N.D. Ill. 2009); Abbott Laboratories v. Baxter, Pharmaceutical Products, Inc., 2005 WL 2347221 (N.D. Ill. 2005); EKR Therapeutics, Inc. v. Sun Pharma., Pharmaceuticals, Ltd., 633 F. Supp. 2d 187 (D.N.J. 2009); Bio-Technology General Corp. v. Duramed, Pharmaceuticals, Inc., 174 F. Supp. 2d 229 (D.N.J. 2001); Bio Technology General Corp. v. Duramed, Pharmaceuticals, Inc., 325 F.3d 1356 (Fed. Cir. 2003); Mead Johnson & Co. v. Barr, Laboratories, Inc., 38 F. Supp. 2d 289 (S.D.N.Y. 1999).

213. 660 F. Supp. 2d 882, 884 (N.D. Ill. 2009).

214. *Id.*

215. *Id.* at 888.

216. 38 F. Supp. 2d 289, 295 (S.D.N.Y. 1999).

217. *Id.* at 296.

remain "highly similar" It is likely to be easier for a follow-on biologic company to change the packaging while remaining "highly similar" than for the follow-on biologic company to change the formulation or manufacturing process while remaining "highly similar."

CONCLUSION

Questions of patent infringement, particularly under the doctrine of equivalents, are difficult even with longstanding, well characterized technologies. The complexities of biotechnology present unique challenges that courts struggle to resolve. The advent of follow-on biologics is yet another hurdle that the legal system is, at the moment, not well positioned to face. Because the development of follow-on biologics is so expensive, it is tremendously important that the products be treated consistently and predictably when they arrive in court.

This Article has presented a guide for industry, courts and scholars on how questions of patent infringement—principally the under doctrine of equivalents—will develop and how they should be resolved. Both the BPCIA and patent law guide the shape of infringement suits. Follow-on biologics companies will be most successful when they make a change in the pre-transformation process, the transformation process, the formulation, or the packaging. They will be least successful when they make a change in the cell culture conditions or the purification process. This is because the FDA will more closely regulate the latter category of changes, giving follow-on biologics companies less scope to make changes that will bring them outside the range of equivalents for the brand-name product. It remains to be seen how courts will address issues of infringement for follow-on biologics, but all parties should be aware of the complexity of the scientific and legal issues and the importance of addressing them properly.