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Christopher M. Holman
University of Missouri - Kansas City, School of Law

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By CHRISTOPHER M. HOLMAN

THE DOCTRINE OF EQUIVALENTS (DOE) allows a court to hold an accused infringer liable for patent infringement in spite of the fact that the accused product (or process) does not fall within the literal scope of the asserted patent claim(s). In the United States, the DOE is judge-made law, rooted in principles of equity and tracing its origins to Supreme Court decisions dating back to the mid-nineteenth century. The 1990s and early 2000s saw a dramatic uptick in interest in the DOE, prompted at least in part by two Supreme Court decisions and an *en banc* Federal Circuit decision specifically addressing the DOE, and more particularly prosecution history estoppel (PHE), a doctrine that imposes significant constraints on the ability of a patentee to assert the DOE, and which can be triggered by a narrowing amendment of a patent claim during patent prosecution, or by arguments made during prosecution.[1] This interest in the DOE manifested itself in a proliferation of law review articles and other legal commentary specifically addressing the application of the DOE and PHE to biomolecules (*i.e.*, proteins and DNA/polynucleotides) and other inventions arising out of biotechnology.

A recurring theme in this commentary is an assumption that claim limitations reciting a protein or polynucleotide are particularly vulnerable to circumvention through the substitution of molecule having a different amino acid or nucleotide sequence, but that allows for substantially the same function as the biomolecule recited in the claim. Given this potential vulnerability to circumvention, the DOE was seen as important means whereby a biotechnology patentee might be able to achieve an adequate scope of protection for claims reciting a specific biomolecule as a significant claim limitation. PHE was something to be avoided if at all possible, on the assumption that the enforceability of a biotechnology patent claim would be substantially impaired if the patentee were limited to the literal scope of the claim, with no opportunity to invoke the DOE in order to expand the effective scope of the claim to encompass functionally equivalent variants.

Perhaps somewhat surprisingly, given the crucial role many commentators attributed to the DOE in the context of biomolecule claim limitations, prior to 2019 the Federal Circuit does not appear to have issued an opinion finding infringement under the DOE in a case in which the relevant claim limitation recites a biomolecule. It finally happened in 2019, however, in the case of *Ajinomoto Co. v. Int'l Trade Comm'n*, with a divided panel of the Federal Circuit holding that a claim limitation reciting a DNA sequence, defined in terms of the amino acid sequence of a protein encoded by the sequence, was infringed under the DOE by a DNA sequence encoding a protein having a different (but similar) amino acid sequence and equivalent function.[2]

In preparing this article, I performed a Westlaw search designed to identify any and all Federal Circuit decisions applying the doctrine of equivalents to a claim limitation reciting a biomolecule, *i.e.*, either a protein or a polynucleotide.[3] I was somewhat

Christopher M. Holman is the Executive Editor of *Biotechnology Law Report* and a Professor at the University of Missouri–Kansas City School of Law.

[1] *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997); *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002); and *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558 (Fed. Cir. 2000) *vacated*, 535 U.S. 722 (2002).

[2] *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342 (Fed. Cir. 2019).

[3] In particular, in December 2019, I performed the following search of all Court of Appeals of the Federal Circuit decisions in the Westlaw database: ("doctrine of equivalents" & (protein or antibody or DNA or gene or polynucleotide or nucleic)). The search yielded 109 decisions. I read enough of each decision to determine whether it met my criterion of applying the doctrine of equivalents (DOE) and/or prosecution history estoppel (PHE) to a biomolecule limitation, in a substantive manner. Most of the 109 decisions did not meet this criterion. All of the decisions that met the criterion are identified and discussed in this article.

surprised at how few cases came up that met the criteria, eight in total pre-dating *Ajinomoto*, including three decisions in which the Federal Circuit found that the DOE was barred by PHE, and two in which the court reached a decision of no infringement under the DOE on the merits. I also found three cases in which a district court found noninfringement under the DOE (twice based on PHE, and once on the merits), and which on appeal were reversed or vacated by the Federal Circuit, but in which the Federal Circuit did not decide the issue of infringement under the DOE.

This article begins with a brief overview of the DOE and PHE, and then turns to a discussion as to why DOE was seen as particularly critical for the enforcement of patent claims reciting biomolecules. It then summarizes and analyzes the Federal Circuit decisions I found in my search that apply the DOE and/or PHE to a claim limitation reciting a biomolecule, concluding with the court's most recent decision *Ajinomoto*.

I. BACKGROUND ON THE DOE

The doctrine of equivalents allows a court to hold an accused infringer liable for patent infringement even though the accused product (or process) does not literally fall within the scope of the asserted patent claims. It has been described as "a judicial response to the practical reality that if a patent can be avoided by copying the claimed invention while making a minor, insubstantial change of just enough scope to take the copied matter outside of the literal boundaries of the claim, the right to exclude that the patent bestows will not be worth very much."[4] In *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, the Supreme Court encapsulated the policy underlying the DOE as "one may not practice a fraud on the patent."[5]

The classic test for infringement under the doctrine of equivalents is the function-way-result (FWR), or tripartite test, which looks to whether an asserted equivalent "performs substantially the same function in substantially the same way to obtain the same result."[6] Historically, the Federal Circuit seemed to view the FWR test as the sole test for equivalence under the DOE, but more recently the Federal Circuit has more often tended to treat the test as merely one way of determining the fundamental question of whether the differences between the claimed invention and the accused device are merely "insubstantial."[7]

The Supreme Court, while acknowledging the critical role that the DOE plays in preventing fraud on patents, has long voiced concern regarding the inherent tension between the DOE and the important role the literal language of patent claims plays in providing notice to third parties of the scope of a patentee's right to exclude. For that reason, the Court has imposed a variety of judicial constraints on the doctrine. In *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, for example, the Supreme Court held that the DOE is to be applied on a claim limitation-by-limitation basis, rather than to the "invention as a whole."[8] In other words, a finding of infringement under the DOE requires that each and every limitation recited in the claim be present in the accused product (or process), either literally or equivalently.

Perhaps the most notable limitation on the DOE is the doctrine of prosecution history estoppel (PHE), which limits the ability of a patentee to ensnare under the DOE any subject matter that is surrendered during prosecution in order to secure allowance of a patent claim. The PHE was the subject of a Supreme Court decision in 1997, *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, in which the Court held that a narrowing amendment of a patent claim made during prosecution creates a rebuttable presumption that the amendment was made for reasons related to patentability, which if unrebutted, bars the application of the doctrine of equivalents as to that element of the claim. The Federal Circuit responded in 2000 with its controversial *en banc* decision in *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.* (*Festo I*), in which the court held that no scope of equivalents survive for any claim limitation that was narrowed during patent prosecution for any reason related to patentability.[9]

In 2002, in its landmark *Festo II* decision, the Supreme Court overturned *Festo I*, jettisoning its irrebuttable presumption that a narrowing amendment absolutely forfeited the DOE with respect to the amended claim limitation, and opting instead for a rebuttable presumption that a narrowing

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[4] JANICE MUELLER, PATENT LAW 665 (5th ed. CCH Inc., 2016).

[5] *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605 (195).

[6] *Id.* at 608.

[7] MUELLER, *supra* note 4, at 671, citing *Hilton Davis Chemical Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1517–18 (Fed. Cir. 1995) (*en banc*).

[8] *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17 (1997).

[9] *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 234 F.3d 558 (Fed. Cir. 2000).

amendment made for reasons of patentability surrenders the particular equivalent in question.[10] The presumption can be rebutted if the patentee can show that "at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent." *Festo II* identified three ways in which a patentee might make this showing, and thereby rebut the presumption that an amendment had resulted in the surrender of a particular equivalent. First, the patentee might show that the equivalent was "unforeseeable at the time of the application." Second, "the rationale underlying the amendment may bear no more than a tangential relation to the equivalent in question." Third, "there may be some other reason suggesting that the patentee could not reasonably be expected to have described the insubstantial substitute in question." These three exceptions to the application of PHE are often referred to as the "foreseeability," the "tangential relation," and the "some other reason" exceptions.

II. THE DOE AND BIOMOLECULES

In the 1990s and early 2000s, a series of law review articles were published that focused specifically on the appropriate scope and application of the DOE with respect to claim limitations reciting a protein and polynucleotide.[11] The authors of these articles assumed that the DOE would play a critical role in the enforcement of patent claims reciting biomolecules. For example, in a 1991 article the author stated that "[b]iotechnology patent owners whose claims were drafted before the early 1980s need to assert the doctrine of equivalents because early claims usually were drafted narrowly."[12] After *Festo II* was decided, an article was published voicing a concern that the decision had saddled patent applicants in the field of biotechnology with "an undue burden: to specifically claim every possible variant of a nucleotide or amino acid sequence or risk a finding in court that minor non-functional substitutions in the claimed sequence were foreseeable," and thus subject to PHE.[13] The authors of this article, patent attorneys working in the field of biotechnology, advised applicants prosecuting biotechnology patents to employee various strategies for avoiding prosecution history estoppel (and thus maintaining access to the doctrine of equivalents), such as including claims of differing scope and language in their initial applications in order to minimize the effect of subsequent claim amendments, avoiding narrowing amendments if possible, and if narrowing amendments are unavoidable, then filing continuation applications to pursue broader claims later.

The assumption that the DOE would play a critical role in the enforcement of patent claims reciting biomolecules was grounded in a recognition that certain requirements of a valid patent claim render it difficult to secure literal patent coverage that is not susceptible to circumvention by altering the sequence of a claimed amino acid or nucleotide sequence.[14] At the heart of this susceptibility to circumvention is the inherent redundancy in the relationship between structure and function in biomolecules. At the polynucleotide level, the redundancy of the genetic code and the possibility of silent codon substitutions allow for an astronomical number of different DNA sequences that encode for the same amino acid sequence. At the protein level, relatively large changes in the amino acid sequence, in the form of amino acid substitutions, deletions, or insertions, can be introduced into a protein without substantially altering its function. A patent claim limited to a single amino acid sequence or gene sequence can be extremely easy to circumvent by making minor changes to the sequence that do not substantially alter the molecule's function. The scope of patent claims can be expanded by drafting claims that encompass these variations, but the

[10] *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002).

[11] *See, e.g.*, Gregory B. Sephton, *Biotechnology: The Doctrine of Equivalents and Infringement of Patented Proteins*, 25 SUFFOLK U. L. REV. 1035 (1991); Michael T. Siekman, *The Expanded Hypothetical Claim Test: A Better Test for Infringement for Biotechnology Patents Under the Doctrine of Equivalents*, 2 B. U. J. SCI. & TECH. L. 52 (1996); 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 (1998); Qing Lin, *A Proposed Test for Applying the Doctrine of Equivalents to Biotechnology Inventions: The Nonobviousness Test*, 74 WASH. L. REV. 885 (1999); Edward R. Jr. Ergenzinger and W. Murry Spruill, *The Doctrine of Equivalents After Festo: A Disparate Impact on Biotechnological Inventions,* 2003 STAN. TECH. L. REV. 2 (2003); J. Jason Lang, *The German Resolution: A Proposed Doctrine of Equivalents Analysis and a Flexible Rule of Prosecution History Estoppel for Biotechnology*, 52 EMORY L.J. 427 (2003).

[12] Sephton, *supra* note 11.

[13] Ergenzinger and Spruill, *supra* note 11.

[14] For a general discussion of the issue, see Christopher M. Holman, *Protein Similarity Score: A Simplified Version of the BLAST Score as a Superior Alternative to Percent Identity for Claiming Genuses of Related Protein Sequences*, 21 SANTA CLARA COMPUTER & HIGH TECH. L.J. 55 (2004).

enablement and written description doctrines constrain the ability of biotechnology patent applicants to broadly claim genuses of related biomolecules. As a consequence, it can be difficult, if not impossible, to secure a valid patent claim that recites a biomolecule in sufficiently broad terms to literally preclude relatively facile circumvention by use of a sequence variant that retains the function of the claimed biomolecule.

III. FEDERAL CIRCUIT DECISIONS ADDRESSING DOE AND BIOMOLECULE CLAIM LIMITATIONS

My Westlaw search, described above, identified a total of eight pre-*Ajinomoto* Federal Circuit decisions, dating back to as early as 1990, that addressed the DOE in the context of a claim limitation reciting a biomolecule. In three of these decisions the court held that PHE applied, and barred the patentee from asserting infringement under the DOE. In two other decisions, a district court held that PHE applied, but the Federal Circuit disagreed, in one case vacating the finding of PHE and remanding for the district court to reconsider the issue, and in the other reversing the district court. In two decisions, the court addressed the merits of an allegation of infringement under the DOE, in both cases finding no infringement under the doctrine. And in one decision, a district court found no infringement under the DOE on the merits on a motion for summary judgment, and the Federal Circuit reversed, holding that factual issues precluded summary adjudication. These eight decisions are summarized below, followed by a summary of *Ajinomoto*, the most recent decision of the Federal Circuit addressing DOE in the context of a biomolecule, and the only one in which an accused infringer was found liable for infringement under the doctrine.

A. Decisions holding that PHE applies

In the following three decisions the Federal Circuit invoked the doctrine of prosecution history estoppel to bar a finding of equivalents with respect to a biomolecule claim limitation.

1. *Regents of the Univ. of California v. Eli Lilly & Co.* The earliest of the three decisions, decided in 1997, was *Regents of the Univ. of California v. Eli Lilly & Co.*.[15] The claims at issue recited genetic constructs (*i.e.*, synthetic DNA molecules) capable of directly expressing human pre-insulin (PI). The Federal Circuit held that the patent owner was estopped from arguing that expression of human PI via a fusion protein intermediate is equivalent to direct expression of human PI, based on amendments to the claims made during prosecution to overcome prior art–based rejections.

In particular, as originally filed some of the claims recited a DNA transfer vector "comprising" a DNA sequence coding for human PI. The claims were rejected as anticipated by prior art teaching the use of recombinant eukaryotic/prokaryotic fusion proteins for the production of a eukaryotic protein, including insulin, in a recombinant bacterium. The patent applicant amended the claims, replacing the word "comprising" with the narrower term "consisting essentially of." The examiner allowed the amended claims, noting that the "consisting essentially of" language "excludes from the [DNA sequence] the presence of sequences other than [those coding for PI]." The Federal Circuit agreed with the district court that this amendment estopped the patent the from arguing that the claim encompassed fusion proteins under the doctrine of equivalents. Note that this case was decided shortly after *Warner-Jenkinson*, and prior to the *en banc* Federal Circuit's *Festo I* decision.

2. *Mycogen Plant Sci., Inc. v. Monsanto Co.* The next decision in which the Federal Circuit found a patent owner estopped from asserting the doctrine of equivalents with respect to a biomolecule limitation was *Mycogen Plant Sci., Inc. v. Monsanto Co.*[16] This case was decided in 2004, shortly after Supreme Court set forth the current standard for assessing PHE in *Festo II*. The patent at issue teaches how to modify a gene that encodes a pesticidal protein of the soil bacterium Bacillus thuringiensis (Bt) for improved expression in plants, allowing for the production of the protein at sufficiently high levels to kill insects. Modifications taught by the patent include altering the codons in the native Bt gene to contain a greater number of codons preferred by the intended plant host than the native bacterial gene prior to modification, while still expressing the same amino acid sequence of the Bt protein. Figure 1 of the patent discloses the DNA sequence of a specific synthetic codon-modified Bt gene engineered for improved expression in a plant host. The claims at issue in the case recite a synthetic gene "comprising the DNA

[15] *Regents of the Univ. of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed. Cir. 1997).

[16] *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 91 F. App'x 666 (Fed. Cir. 2004).

sequence presented in FIG. 1," *i.e.*, the specific codon-modified Bt gene disclosed in the patent.

The DNA sequences of Monsanto's accused genes were significantly different than the sequence presented in FIG. 1 of the patent, clearly precluding a finding of literal infringement, as decided by the district court on a motion for summary judgment and affirmed by the Federal Circuit. But Monsanto's genes were synthetic codon-modified Bt genes modified to contain a greater number of plant-preferred codons, as taught by the patent specification. In particular, the accused genes were about 78 percent homologous to the native Bt gene on which they were based, and employed plant-preferred codons at a frequency of about 51 percent. The patent owner, Mycogen, argued that Monsanto's modified Bt genes infringed under the doctrine of equivalents, but the district court held that PHE barred Mycogen's assertion of infringement under the DOE, and on appeal the Federal Circuit affirmed.

During prosecution, the patent application that ultimately issued as Mycogen's patent included the following claims broadly reciting structural variants of a Bt gene designed for improved expression in plants:

> 1. A synthetic gene designed to be highly expressed in plants comprising a DNA sequence encoding an insecticidal protein which is functionally equivalent to a native insecticidal protein of Bt.
> 2. A synthetic gene of claim 1 wherein said DNA sequence is at least about 85% homologous to a native insecticidal protein gene of Bt.
> 5. A synthetic gene of claim 1 wherein the overall frequency of preferred codon usage within the entire coding region of said synthetic gene is within about 75% of the frequency of codon usage preferred in plants.
> 6. A synthetic gene of claim 1 wherein the frequency of preferred codon usage within the entire coding region of said synthetic gene is within about 90% of the frequency of codon usage preferred in plants.

Mycogen canceled all of these claims after they were rejected for lack of enablement, with the examiner asserting that "the disclosure is enabling only for claims limited to claims which recite the sequence shown in Figure 1[sic]." In assessing the scope of PHE, the Federal Circuit found it significant that these canceled claims were broader than the claims asserted by Mycogen against Monsanto, but yet still not broad enough to encompass the accused Monsanto genes.

Applying *Festo II*, the Federal Circuit found it immaterial that the claims at issue were not themselves amended to avoid patentability rejections, because broader claims which addressed the same claim limitations at issue in this case, *i.e.*, gene homology and preferred codon usage, had been canceled in response to a rejection for unpatentability, namely a failure to enable anything other than the recited sequence in Figure 1. The cancellation of the broader claims created a rebuttable presumption that all subject matter between the pertinent limitations of the original claims and those of the final, issued claims was surrendered.

Invoking *Festo*'s foreseeability exception, Mycogen argued that it should be permitted to present extrinsic evidence that the accused equivalent in this case, namely a gene with approximately 78 percent homology with the native Bt gene, and having a plant-preferred codon usage of 51 percent, was unforeseeable at the time of patenting. However, the Federal Circuit held that the fact that Mycogen originally claimed coverage of genes bearing 85 percent similarity to the native Bt gene provides evidence that the applicants foresaw the possibility of less homologous genes. Moreover, Mycogen originally attempted to claim all functionally equivalent genes in original independent claim 1. Mycogen clearly tried, unsuccessfully, to obtain coverage of the least homologous genes that it could claim, but was repeatedly unable to satisfy the rejections of the examiner for anything broader than the specific gene listed in Figure 1. Thus, broader coverage was clearly foreseeable, yet unattainable in light of the patent's limited disclosure.

Turning to *Festo*'s tangential exception, Mycogen argued that the reason for the cancellation of claims 1, 2, 5, and 6 was merely tangential to achieving a patentable invention because Mycogen successfully obtained broader product-by-process claims in different patents, which were held to be infringed by Monsanto's product. The court rejected this argument, finding "no legal support for the proposition that obtaining broader claims of a different nature has the effect of broadening the range of equivalence available to all claims, including product claims, when those product claims have been effectively narrowed by claim cancellation."

In short, Mycogen was estopped from asserting the DOE against Monsanto because the company had narrowed the scope of its claim coverage vis-à-vis the nucleotide homology and the frequency of plant-preferred codon usage.

3. *Amgen Inc. v. Hoechst Marion Roussel, Inc.* In *Amgen Inc. v. Hoechst Marion Roussel,*

Inc., decided in 2006, the relevant claims at issue were product claims 2–4 of U.S. Patent No. 5,621,080 ("the '080 patent"), directed towards glycosylated erythropoietin (EPO).[17] These claims all included the limitation that the "erythropoietin glycoprotein comprises the mature erythropoietin amino acid sequence of FIG. 6." Figure 6 of the patent discloses a DNA sequence coding for a protein consisting of 166 amino acids, which is the form of the native human protein as it is initially synthesized in a human cell. Mature human EPO, on the other hand, actually contains only 165 amino acids, because the 166th amino acid, arginine, is cleaved off prior to secretion of the protein from the cell. The question before the court was whether prosecution history estoppel barred Amgen from claiming that the asserted claims encompasses Hoechst Marion Roussel's (HMR's) accused EPO product, which was mature and thus only consisting of 165 amino acids, under the doctrine of equivalents.

The prosecution history of Amgen's claims is quite complex, but essentially the court found that as initially filed the patent application claimed proteins having the sequence of both human and non-human monkey EPO, as well as "a fragment" of the human EPO. The court further found that, in order to overcome a double-patenting rejection, which the court found to be related to patentability under *Festo* II, the applicant had amended the claim to recite only a human EPO product having the complete amino acid sequence of Figure 6, *i.e.*, the 166 amino acid sequence, creating a presumption of estoppel with respect to HMR's accused 165 amino acid sequence.

The district court determined that Amgen had failed to show that a 165 amino acid form of EPO was unforeseeable at the time of the amendment, and thus *Festo*'s unforeseeability exception did not apply. However, the district court went on to find that Amgen had succeeded in rebutting the presumption of PHE through the tangential exception, because the amendment was only intended to limit the claims to human EPO products, not to limit the number of amino acids, and that there was no more than a tangential relationship between the amendment and the equivalence of a 165 amino acid EPO.

On appeal, the Federal Circuit affirmed with respect to the unforeseeability exception, agreeing that the 165 amino acid version of EPO was a foreseeable equivalent because the patentee admittedly knew about the 165 amino acid equivalent at the time of the narrowing amendment. The Federal Circuit disagreed with the district court, however, with respect to the tangential exception, and held that Amgen had not only amended the claims to limit them to human EPO products, but had also narrowed the claim so as to not cover fragments of the 166 amino acid EPO sequence disclosed in Figure 6. The Federal Circuit found that narrowing the claim to exclude fragments of the 166 amino acid EPO "may have been central" to overcoming the double-patenting rejection, and not merely tangential to the question of whether the 165 amino acid accused product infringed, since removal of the arginine essentially created a fragment of the full-length amino acid sequence. The court further found that if the patentee had wished only to limit the claims to human EPO, without disclaiming fragments, the patentee could have done so by continuing to use the adjective "human" when referring to EPO in the amended claims, but instead chose to further narrow the claims by making reference to the specific sequence in Figure 6.

The district court had also set forth an alternate rationale under *Festo*'s "some other reason" exception for finding that Amgen had overcome the presumption of PHE, based on the fact that, before the amendment was introduced, Amgen disclosed information to the Patent and Trademark Office (PTO) concerning the fact that mature human EPO consists of only165 amino acids. The district court also relied on extrinsic evidence that a person of ordinary skill in the art would understand that Amgen meant to claim human EPO having either 165 or 166 amino acids at the time of the amendment. The court reasoned that Amgen had rebutted the *Festo* presumption under the "some other reason" criterion because the patentee could not have reasonably been expected to have described the 165 amino acid equivalent, because those of skill in the art would have interpreted the amendment to cover the 165 amino acid equivalent.

The Federal Circuit disagreed, however, finding that the district court's analysis had not correctly applied the Supreme Court's explanation of the "some other reason" rebuttal argument, pursuant to which the "other reason" must be of such a nature that the patentee could "not reasonably be expected" to write a claim to encompass the equivalent, such as a shortcoming of language. The court found that Amgen knew of the 165 amino acid sequence at the time of the amendment, but chose to limit the claims to the 166 amino acid sequence depicted in Figure 6, and that whether the patentee,

[17] *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293 (Fed. Cir. 2006).

the examiner, or a person of skill in the art may have thought the claims encompassed EPO with 165 amino acids does not excuse Amgen's failure to claim the equivalent. Further, there were no shortcomings of language that might have prevented Amgen from claiming EPO having 165 amino acids. The patentee could have simply claimed mature human EPO without reference to Figure 6. Alternatively, the patentee could have claimed EPO having the amino acid sequence disclosed in Figure 6 or a "fragment thereof." In short, there was no linguistic barrier to claiming EPO comprised of 165 amino acids.

Having failed to qualify for any of the *Festo* exceptions, Amgen was held to be barred by PHE from asserting equivalents with respect to the accused 165 amino acid form of EPO.

B. Decisions overturning a district court's finding of PHE

In the following two decisions a district court invoked the doctrine of prosecution history estoppel to bar a finding of infringement under the DOE with respect to a biomolecule claim limitation, but on appeal the Federal Circuit vacated or reversed the district court's decision.

1. *Hormone Research Found., Inc. v. Genentech, Inc.* The earliest Federal Circuit decision I could find addressing PHE or DOE in the context of a biomolecule limitation was *Hormone Research Found., Inc. v. Genentech, Inc.*, decided in 1990.[18] The relevant claim limitation recites a product having "a structure corresponding to FIG. 2" of the patent. Figure 2 discloses the amino acid sequence of a synthetic version of human growth hormone (hGH) that was synthesized by the patent applicant, and which at the time was thought to be sequence of naturally occurring hGH. Later, it was found that the amino acid sequence of natural hGH is slightly different than that set forth in Figure 2. The district court found that the accused product, a recombinantly produced hGH having the same sequence as native hGH, did not literally infringe, because the literal scope of the asserted claims was limited to a material having the "exact structure and conformation" shown in Figure 2, *i.e.*, the amino acid sequence of the synthetic hGH. On appeal, the Federal Circuit affirmed with respect to the finding of no literal infringement.

The district court also found that PHE precluded the patent owner from asserting the DOE, but the Federal Circuit reversed on this issue and remanded for reconsideration. The district court's finding of PHE was not based on any amendment of the claims, but rather on arguments made by the patent applicant to overcome a prior art reference. In particular, in the course of arguing that prior art identified by the examiner did not anticipate the claims, the applicant stated that the claims are "limited to the structures shown in the drawings and are not directed broadly to hGH or its derivatives," and that "these product claims are specific to the chemical formula of Fig. 2 or Fig. 3, and the reference does not show the same."

On appeal, the Federal Circuit found that the district court interpreted these statements to mean that the pending claims were confined to the specific structure of Figure 2 and that the prior art reference was not anticipatory because it depicted the different, although very close, structure of natural hGH. The Federal Circuit found that, if it were clear that this was the message that the applicant's arguments were intended to convey, the district court's determination that the prosecution history precludes the patentee from recovering under the doctrine of equivalents would be correct.

But the Federal Circuit found that there were other plausible interpretations of the statements made by the applicant in arguing that the claims were not anticipated by the prior art, and that these alternate interpretations would not necessarily lead to a conclusion of prosecution history estoppel. For example, the applicant might have only intended to surrender molecules derived from natural HGH, or might have intended to suggest that the prior art was not anticipatory of the rejected claims because it was not enabling under 35 U.S.C. § 112, since it did not disclose a structure of, or how to make, hGH. The Federal Circuit held that the existence of disputed factual questions regarding the intent and meaning of the prosecution arguments precluded summary judgment, and vacated the district court's finding of prosecution history estoppel.

2. *Intervet Inc. v. Merial Ltd.* In *Intervet Inc. v. Merial Ltd.*, the claim at issue recites a "vector comprising an isolated DNA molecule comprising a sequence selected from the group consisting of ORFs [open reading frames] 1 to 13 of porcine circovirus type II [PCV-2]."[19] The invention was based on the discovery of a new type of pathogenic viruses, which was dubbed PCV-2, to distinguish it from a previously identified and related, but non-pathogenic, type of PCV referred to as type I,

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[18] *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558 (Fed. Cir. 1990).

[19] *Intervet Inc. v. Merial Ltd.*, 617 F.3d 1282 (Fed. Cir. 2010).

or PCV-1. The patent discloses PK/15, a DNA sequence previously identified and isolated from pig kidney cells, as a representative example of a PCV-1 virus. The patent further discloses five isolated pathogenic porcine circovirus strains that are identified as representative of type II, *i.e.*, PCV-2. In particular, the patent specification provides DNA sequences for the genomes of four PCV-2 strains, and observes that the sequenced PCV-2 strains exhibit 96 percent nucleotide homology with each other, and only 76 percent nucleotide homology with PK/15, the representative PCV-1 strain.[20] The specification also identified thirteen ORFs in the PCV-2 genomes, nine of which are unique to PCV–2, and four that are present in both PCV–2 and PCV–1.[21]

The allegedly infringing vaccine, produced by Intervet, contained a nucleotide sequence that was 99.7 percent homologous to one of the PCV-2 sequences disclosed in the specification. The district court held that there was no literal infringement because the sequence was not identical to any of the PCV-2 sequences provided in the patent. The district court further found that PHE prevented the patent owner from asserting infringement under the DOE. On appeal, the Federal Circuit held that the district court had erred in finding that PHE precluded Merial from arguing that the accused product was equivalent to one of the ORFs recited in the claim, and instructed the district court on remand to consider whether the claim was infringed under the DOE.

As originally drafted, the claim recited a "vector comprising an isolated DNA molecule comprising a sequence selected from the group consisting of ORFs 1–13." The examiner rejected this claim in view of ORFs from PK/15, noting that for purposes of the rejection "[t]he ORFs are assumed to be derived from porcine circovirus, but as written, the claims could encompass ORFs from any organism." The applicant amended the claim to add the limitation that the recited ORFs were "of porcine circovirus type II," at which point the claim was allowed.

The Federal Circuit agreed with the district court's conclusion that the amendment was substantially related to patentability, thus raising a presumption of surrender for all equivalents residing in the territory between the identified ORFs of PCV–2 and ORFs of PCV–1, as well as corresponding ORFs, if any, for any non-porcine organism. Merial was thus estopped from arguing that ORFs of pathogenic circoviruses found in other organisms are equivalent to ORFs of PCV–2. It was also estopped from arguing that ORFs of a pathogenic strain of PCV–1 having strong homology with PK/15 and weak homology with the representative PCV-2 strains disclosed in the patent are equivalent to ORFs of PCV–2. Merial was not, however, estopped from arguing that a pathogenic porcine viral sequence with over 99 percent nucleotide homology with one of the five representative strains is equivalent to that strain. The Federal Circuit found that, under *Festo II*, "such a draconian preclusion would be beyond a fair interpretation of what was surrendered." In the view of the Federal Circuit, the rationale underlying the amendment was to narrow the claimed universe of ORFs down to those of PCV–2, and bore only a tangential relation to the question of which DNA sequences are, and which sequences are not, properly characterized as PCV–2.

C. Decisions finding no infringement under the DOE

In the following two decisions the Federal Circuit addressed the merits of an assertion of infringement under the DOE, with respect to a biomolecule claim limitation, and held that there was no infringement.

1. *Genentech v. Wellcome*. The first Federal Circuit decision to meet these criteria was *Genentech v. Wellcome*, one of the seminal decisions of biotechnology patent law.[22] There were three patent claims at issue in the case, all relating to human tissue plasminogen activator (human t-PA), referred to herein as the "protein claim," the "cell culture claim," and the "process claim."

The "protein claim" recites "human plasminogen activator, having thrombolytic properties, immunologically distinct from urokinase and having a specific activity of about 500,000 IU/mg. using the WHO First International Reference Preparation of t–PA (tissue plasminogen activator) as assay standard or a specific activity of about 90,000 IU/mg. using the WHO First International Reference Preparation of urokinase as assay standard."[23]

The "cell culture claim" recites a "cell culture capable of expressing human tissue plasminogen activator, obtained by transforming a mammalian cell line with a ... recombinant expression vector containing a DNA sequence encoding human tissue plasminogen activator, wherein the vector is capable

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[20]The court uses the term homology, but defines it to mean identity.

[21]An ORF is a portion of a gene that contains a sequence of nucleotide bases that may be translated into a protein.

[22]*Genentech, Inc. v. Wellcome Found. Ltd.*, 29 F.3d 1555 (Fed. Cir. 1994).

[23]U.S. Patent 4,752,603, claim 1.

of expressing human tissue plasminogen activator in a transformed microorganism or cell culture."[24]

The "process claim" recites a "process for producing recombinant human tissue plasminogen activator comprising: (a) growing recombinant cells in a growth medium, said cells being a microorganism or cell culture transformed with an expression vector containing DNA encoding human tissue plasminogen activator; and (b) simultaneously expressing said DNA, thereby producing recombinant human tissue plasminogen activator."[25]

The accused product at issue in the case was identified as FE1X, a recombinant version of human t-PA that was structurally distinct from natural t-PA in ways intended to render it superior as a human therapeutic (used to treat heart attack). The amino acid sequence of natural t-PA consists of five separate domains, each having different functional attributes: the Finger (F) region, the Epidermal Growth (E) region, the Kringle 1 (K1) region, the Kringle 2 (K2) region, and the Serine Protease (P) region. The FE1X protein takes its name from the fact that it lacks the Finger (F) region and most of the Epidermal Growth (E) region of natural t-PA, and eliminates one of the carbohydrate chains by altering the protein at position 117 of the K1 region (where glutamine is substituted for arginine), thereby changing the glycosylation pattern (1X). It also has a different amino acid at position 245.

On a motion for summary judgment, the district court found that FE1X did not literally infringe the protein claim, and that the processes and reagents used to produce recombinant FE1X did not infringe the cell culture or process claims. All three of the claims included the term "human plasminogen activator" or "human tissue plasminogen activator," which the court interpreted as limited to the genus consisting of the full-length amino acid sequence of human t-PA and any "naturally-occurring allelic variant" thereof. FE1X does not literally fall within this definition. However, the jury found that FE1X infringed all three of the claims under the DOE, and the trial court denied the accused infringer's motion for judgment as a matter of law (JMOL) of noninfringement.

On appeal, the Federal Circuit reversed, finding that the trial judge should have granted JMOL in favor of the accused infringer on the DOE finding by the jury. The DOE analysis focused on two limitations appearing in the claims: (1) the "specific activity limitation" recited in the protein claim, which limited the claim to a tissue plasminogen activator "having a specific activity of about 500,000 IU/mg"; and (2) the "human tissue plasminogen activator limitation," which limited the cell culture and process claims to recombinant cells "containing a DNA sequence encoding human tissue plasminogen activator" and thereby "capable of expressing human tissue plasminogen activator."

The court's analysis of the human t-PA relied solely on the function-way-result test, which the court held required a showing of substantial identity of function, way, and result in order to support a finding of equivalency. At the outset of its analysis, the court explicitly recognized that there are a variety of ways to define the function of a protein, some quite broad and others relatively narrow, and that the outcome of the analysis will hinge upon how function is defined. In denying JMOL, the trial court had assumed a broad definition of the function of human t-PA, which is to stimulate "the dissolution of fibrin clots through the cleavage of plasminogen to plasmin." But the Federal Circuit took issue with this definition, finding it "difficult to imagine how FE1X, or any version of t-PA for that matter, 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 general results."

Instead, the Federal Circuit opted for a narrower definition of function, which requires a t-PA to not only catalyze the conversion of plasminogen to plasmin, but also to bind to fibrin. The court pointed to *Graver Tank* for the proposition that the "operative definition for purposes of equivalency analysis is the intended function as seen in the context of the patent, the prosecution history, and the prior art." According to the court, this was the definition of t-PA as set forth in the specification, with the specification expressly defining fibrin binding as a critical component of the "function" of human t-PA. The court found this interpretation to be supported by not only the specification, but also extrinsic evidence, including a British patent application filed by one of the accused infringers, which identified fibrin binding as a therapeutically critical function of human t-PA, because it reduces the risk of hemorrhaging. Moreover, two of the inventors testified that the fibrin binding affinity of human t-PA is a critical distinction between this protein and the two plasminogen activators, urokinase and streptokinase, that were known to the prior art. The court pointed out that a functional definition of t-PA

[24]U.S. Patent 4,766,075, claim 8.
[25]U.S. Patent 4,853,330, claim 8.

that did not include fibrin binding would result in a range of equivalents that impermissibly encompassed these prior art proteins. In short, the court found that the "function" of human t-PA for the purposes of equivalency analysis includes fibrin binding, and no reasonable jury could have concluded otherwise.

Turning to the "way" and "result" prongs of the tripartite test, the court found the record to be devoid of any particularized evidence or linking argument showing that FE1X functions in substantially the same way as human t-PA or achieves substantially the same results. Although the patent owner pointed to testimony of several witnesses to the effect that the Kringle 2 (K2) region of amino acids is present in both FE1X and human t-PA, and that this region plays a role in the ability both to bind fibrin, the court found this testimony to be "speculative ... tentative and conclusory."

The court went on to find that, even if one were to assume that the K2 region retained in FE1X plays some role in the binding of fibrin, this would hardly establish that the native t-PA and FE1X "bind to fibrin is substantially the same way with substantially the same results, particularly in view of the overwhelming and undisputed evidence that the two possess dramatically different properties and structure." First, there was undisputed testimony that the fibrin binding affinity of FE1X is less than half that of human t-PA. Second, there was undisputed evidence showing that an amino acid substitution in FE1X would eliminate a glycosylation site, substantially altering the mode of binding. And third, there was undisputed evidence that FE1X behaved significantly different than human t-PA in the human body. In particular, FE1X has a half-life about 10x that of natural t-PA, and has a significantly decreased affinity for binding to endothelial cells in relation to human t-PA. In short, the alterations that rendered FE1X a better therapeutic molecule than its natural counterpart also rendered the molecule substantially different for purposes of equivalence under the DOE.

In closing, the Federal Circuit noted:

> We are mindful that the state of the science in this area of endeavor is very imprecise. Thus, it would be inappropriate to [require] plaintiffs/appellees to prove the specific mechanism by which FE1X binds to fibrin, or to prove that the different properties and structure exhibited by FE1X bear no relation to the binding function. Our only point is that the showing that the K2 region plays a role in the binding function of each is insufficient, particularly in view of the profound differences in the properties and structure possessed by each.[26]

Having thus found the cell culture and process claims not infringed under the DOE, the court turned its attention to the remaining protein claim. Although this claim recited "human plasminogen activator," the court found it unnecessary to reach a conclusion as to whether FE1X is equivalent to human plasminogen activator, instead basing its finding of noninfringement under the DOE on its analysis of the "specific activity" limitation. Specific activity is a measure of protein purity, based on the amount of protein activity per milligram of protein in a sample. The protein claim did not originally include the specific activity limitation, but it was added during prosecution in order to distinguish the claim over prior art. In particular, prior art attributable to one of the named inventors disclosed purified human t-PA having a specific activity of 266,000 IU/mg, and a rejection based on this prior art was overcome by adding a limitation of a specific activity of "about 500,000 IU/mg." The court found that the only evidence in the record regarding the specific activity of FE1X showed the specific activity of FE1X to be approximately 253,800 IU/mg, i.e., essentially the same as the prior art, and that no reasonable jury could have concluded that the patent owner was not estopped from arguing that a plasminogen activator with roughly the same activity as the prior art, which was avoided by the amendment to the claim, infringes under the DOE.

Judge Lourie, the Federal Circuit judge who took the leading role in the Federal Circuit's early biotech jurisprudence, joined the majority's opinion, but filed a concurrence arguing for a different framework for analyzing a DNA or protein for equivalence under the DOE.[27] He argued that, under *Graver Tank*, an accused compound can be found to infringe if it represents only an insubstantial change from the claimed compound. In his view, the difference between FE1X and native t-PA is substantial given that FE1X has 15 percent fewer amino acids, *i.e.*, 446 v. 527, and ten times the half-life of natural t-PA. He further found that FE1X was not the product of copying, but rather a very different material, "independently invented and developed, requiring an estimated 130 man-years, and costing

[26] 29 F.3d at 1569.
[27] 29 F.3d at 1570.

$20 million. If claims are to have any meaning, as a matter of law such a substance cannot be held to be infringing."

He concluded his concurrence with the following observation:

> [T]his case illustrates the problem that results ... when the fact-finder unduly focuses only on the function, way, result analysis of *Graver Tank*. These limited means of analysis fail to fully elucidate the issue, especially when the patented material is a chemical, as it is here. Is the increased half-life part of the "way" analysis or is it a different "result"? Is the binding to fibrin "function," as stated by the majority, or is it part of the "way" t-PA dissolves clots? These questions illustrate the shortcomings of the function, way, result tests which relate to "how" a substance works, *i.e.*, what it does, rather than what it is, which claims purport to define. The other aspects of *Graver Tank*, if properly considered by the fact-finder, would have led to a sounder result. The substantiality of the difference between the accused and claimed compounds, the fact of independent development, and the lack of copying, all lead to a conclusion of lack of infringement.[28]

Thus, in Judge Lourie's view, the tripartite test for equivalence is not necessarily the best way to address the ultimate question of whether an element in an accused product or process is equivalent to a claim limitation, especially when the patented material is a chemical, such as a protein or DNA molecule. He suggested that "substantiality of the difference" would be a better test, and indeed it would not be too long before the Federal Circuit acknowledged that the tripartite test is not the sole test for doctrine of equivalents analysis, and that substantiality of the difference is oftentimes the more appropriate test.[29]

2. *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.* After *Genentech v. Wellcome* the Federal Circuit did not address the merits of a claim of equivalence under the DOE with respect to a biomolecule claim limitation again until 2008, in the case of *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, wherein the court affirmed a district court's decision that a thermophilic Thermus aquaticus (Taq) DNA polymerase gene was not equivalent to a claim limitation requiring a gene derived from E. Coli.[30] The claim at issue recited a "recombinant plasmid containing a DNA coding sequence for the expression of DNA polymerase activity [derived from E. coli]."[31] The accused product was engineered to contain a DNA polymerase gene derived from the Taq bacterium, produced using a recombinant plasmid containing the *Taq* polymerase gene. The district court found no infringement under the doctrine of equivalents.

On appeal, the patent owner argued that substitution of the Taq gene for the E. coli gene was an insubstantial and unimportant change that resulted in an infringing equivalent. The Federal Circuit, however, agreed with the District Court, holding that the "all limitations rule" restricts the doctrine of equivalents by preventing its application when doing so would vitiate a claim limitation, and that in determining whether a finding of infringement under the doctrine of equivalents would vitiate a claim limitation, one must consider "the totality of the circumstances of each case and determine whether the alleged equivalent can be fairly characterized as an insubstantial change from the claimed subject matter without rendering the pertinent limitation meaningless."

The court went on to find that a finding that Taq is an equivalent of E. coli would essentially render the "bacterial source [is] E. coli" claim limitation meaningless, thereby vitiating it. The court observed that "in drafting the claims, the patentees specifically chose to limit [the claim] to a recombinant plasmid where the bacterial source is E. coli. Appellants cannot now argue that any bacterial source, including Taq, would infringe that claim. Accordingly, summary judgment of noninfringement was appropriate."[32]

D. A decision reversing a district court's finding of no infringement on the merits

My search identified one decision, *Goldenberg v. Cytogen*, in which the district court, on a motion for

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[28] *Id.*

[29] *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512 (Fed. Cir. 1995) (*en banc*); *See also Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1351 (Fed. Cir. 2003) ("Under the doctrine of equivalents, a claim limitation not literally met may be satisfied by an element of the accused product if the differences between the two are 'insubstantial' to one of ordinary skill in the art. While no particular linguistic framework controls the inquiry, the insubstantial differences inquiry may be guided by determining whether the element in the accused device 'performs substantially the same function in substantially the same way to obtain the same result' as the claim limitation.") (citing *Graver Tank*).

[30] *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115 (Fed. Cir. 2008).

[31] U.S. Patent 6,017,745, claim 4.

[32] 541 F.3d at 1139.

summary judgment, found noninfringement under the DOE on the merits, but the Federal Circuit reversed that decision. The district court's grant of summary judgment was based on its unfounded belief that the asserted equivalent was a cell surface antigen, which could not, in that court's view, perform the same "function" in the same "way" as "an antigen located within a tumor cell."[33] On appeal, the Federal Circuit faulted the district court's conclusion for being based on a faulty premise, *i.e.*, that the asserted equivalent was a cell surface antigen, when in fact it was a transmembrane antigen. In the view of the Federal Circuit, the district court had erred by engaging in "black and white categorization," in assuming that an antigen must be either intracellular or located on the cell surface, when in fact there are transmembrane antigens that fall into a "grey" category. The court found that the question of whether a transmembrane engine can be equivalent to an antigen located within tumor cell was a factual issue that cannot be decided on summary judgment.

E. Ajinomoto Co. v. Int'l Trade Comm'n

The most recent Federal Circuit decision meeting the criteria, *Ajinomoto Co. v. Int'l Trade Comm'n*, was decided in August of 2019. In this case the Federal Circuit for the first time found infringement under the DOE in a case where the claim limitation recites a biomolecule, more specifically a DNA sequence encoding a protein.[34] This was a split decision, with a dissent arguing that a finding of infringement under the doctrine of equivalents was barred by prosecution history estoppel.

The patent at issue provides an improved fermentation process for producing an aromatic L-amino acid, such as L-tryptophan, which involves the use of a recombinant E. coli bacterium that has been engineered to express higher than natural levels of YddG, a membrane protein that transports aromatic L-amino acids out of the bacterial cell and into the surrounding culture medium. The patent discloses and claims several means for achieving enhanced YddG activity, but in this article I will focus on the means which was relevant for the issue of DOE, which is through the introduction of multiple copies of a DNA sequence encoding the YddG protein into the chromosome of a bacterium to express greater amounts of YddG than would be expressed naturally. The claim at issue defines the DNA sequence encoding the YddG protein as either (1) DNA encoding a protein having the amino acid sequence of SEQ ID NO: 2 (*i.e.*, the amino acid sequence of native E. coli YddG), or (2) a nucleotide sequence which hybridizes under stringent conditions with the complement of the nucleotide sequence of SEQ ID NO: 1 (*i.e.*, the nucleotide sequence of the native E. coli yddG gene).

The DOE issue in the case centered around two strains of genetically engineered E. coli that were accused of infringing the patent claim, which the court referred to as the "first later strain" and a "second later strain." The chromosome of each of these strains had been engineered to contain, in addition to the native E. coli yddG gene, a second gene encoding a YddG protein from a non-E. coli bacterium. This non-E. coli YddG performs the same function as its E. coli counterpart, but has a slightly different amino acid sequence. In the "first later strain," the second gene is the native gene derived from the non-E. coli bacterium that naturally expresses the non-E. coli YddG protein. In the "second later strain," the second gene is a codon-randomized version of the non-E. coli Yddg gene used in the "first later strain." The second gene encodes the exact same amino acid sequence in both strains, but the DNA sequence used in the second strain has been altered by the introduction of silent mutations, substituting degenerate codons for those that appear naturally in the non-E. coli gene.

In order to understand the prosecution history estoppel issues raised in the case, some background on the prosecution of the patent is in order. As originally filed, the claim defined the DNA encoding the YddG protein as either (1) DNA encoding a protein that consists of the amino acid sequence of SEQ ID NO: 2 (*i.e.*, the amino acid sequence of natural E. coli YddG), or (2) "a protein which comprises an amino acid sequence including deletion, substitution, insertion or addition of one or several amino acids in the amino acid sequence shown in SEQ ID NO:2." Whoever drafted the claims was obviously concerned that a claim limited to the exact amino acid sequence of natural E. coli YddG could be circumvented by use of a protein having a slightly different amino acid sequence but retaining substantially the same function, and sought to broaden the definition of the protein to encompass "one or several" amino acid alterations relative to the native gene.

During prosecution, the patent examiner rejected the claim as anticipated by a reference that

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[33] *Goldenberg v. Cytogen*, 373 F.3d 1158 (Fed. Cir. 2004).

[34] *Ajinomoto Co. v. Int'l Trade Comm'n*, 932 F.3d 1342 (Fed. Cir. 2019). An edited copy of this decision is provided in the "Case in Point" section accompanying this article in *Biotechnology Law Report*.

disclosed a recombinant E. coli bacteria comprising a DNA sequence encoding the E. coli "yfiK gene product" (*i.e.*, the E. coli YfiK protein), which presumably has an amino acid sequence similar but not identical to the YddG protein. The use of the term "several" in the claim limitation creates the potential for some ambiguity as to the number of amino acid variations that would fall within the literal scope of the claim, but the specification provides: "Although the number of 'several' amino acids differs depending on the position or the type of amino acid residues in the three-dimensional structure of the protein, it may be 2 to 30, preferably 2 to 15, and more preferably 2 to 5 for the protein."

Giving the claim its broadest reasonable interpretation, which is the appropriate standard during the examination of pending patent claims, the examiner should have found that the claim literally encompasses variance of up to 30 amino acids from the sequence of native E. coli YddG protein, which would presumably encompass the prior art YfiK protein. The applicant could have responded by amending the claim so as to reduce the number of amino acid variations encompassed by the claim, in a manner that would exclude the YfiK protein from the scope of the claim. Instead, the applicant abandoned this approach to achieving claim breadth altogether, and switched over to an approach that focuses on sequence similarity in the DNA sequence rather than the amino acid sequence of the encoded protein. In particular, the applicant amended the claim by replacing part (b) of the definition with "a protein which comprises an amino acid sequence that is encoded by a nucleotide sequence that hybridizes with the nucleotide sequence of SEQ ID NO:1 (*i.e.*, the E. coli YddG gene) under stringent conditions." The claim was thus amended to encompass genes capable of hybridizing to the E. coli YddG under conditions that are "stringent," as that term is defined in the specification. DNA sequences will only hybridize to each other under stringent conditions if they share a relatively high degree of sequence similarity, so the ability to hybridize basically serves as a proxy for DNA sequence similarity. Particularly in the early days of biotechnology patenting, this sort of hybridization language was routinely used in an attempt to expand the literal coverage of claims directed towards genes and other DNA molecules, in an attempt to encompass variants differing from the literally disclosed sequence, but sharing some degree of sequence similarity.

In proceedings before the International Trade Commission (ITC), the Commission found the "first later strain" to be literally infringing, based on its determination that the non-E. coli yddG gene satisfied part (2) of the definition of a DNA encoding the YddG protein, *i.e.*, the nucleotide sequence of the non-E. coli gene would hybridizes under stringent conditions to the E. coli yddG gene. This finding of literal infringement was not a subject of the appeal and was not directly discussed by the Federal Circuit, but was relevant to the DOE analysis discussed below.

The "second later strain," on the other hand, was not found by the Commission to literally infringe, presumably because the codon-randomized non-E. coli gene was sufficiently different in sequence that it would not hybridize under "stringent conditions" to the E. coli gene. The Commission went on to find, however, that the "second later strain" infringed under the DOE, based on its determination that the codon-randomized non-E. coli gene introduced into the genome of the second later strain is equivalent under the DOE to the nucleotide sequence defined by part (1) of the definition of a DNA encoding the YddG protein. In other words, the amino acid sequence encoded by the codon-randomized gene was found to be equivalent to the amino acid sequence of natural E. coli YddG.

On appeal, the Federal Circuit began by considering whether the doctrine of PHE barred a finding of infringement under the DOE. The Federal Circuit panel was divided on this issue, with the majority holding that PHE did not apply in this case, while the dissent argued that it did. The views of both the majority and dissent are summarized below.

Applying *Festo*, the majority found that, although the narrowing amendment had created a presumption of PHE, the presumption had been rebutted under the "tangential relation" exception. In particular, the court found that the

> objectively evident rationale for the amendment was to limit the set of proteins within the claim's scope so that it no longer included the prior-art E. coli YfiK protein and, more generally, no longer allowed as wide a range of amino acid alterations (hence changes in the protein) as original alternative (B), which had allowed "deletion, substitution, insertion or addition of one or several amino acids in the amino acid sequence shown in SEQ ID NO: 2." The reason for the amendment had nothing to do with choosing among several DNA sequences in the redundant genetic code that correspond to the same protein.

The majority pointed out that the native non-E. coli gene used in the "first later strain" fell within the literal scope of the claim, presumably

due to the similarity of the E. coli and non-E. coli gene sequences, which would result in hybridization under stringent conditions, and that the native non-E. coli gene of the "first later strain" encoded a protein having an identical amino acid sequence to the codon-randomized non-E. coli gene present in the "second later strain." Since the proteins encoded by the two genes were identical, the only difference was in codon usage, and the majority concluded that the reason for the amendment had nothing to do with narrowing the claim with respect to codon usage.

Moving to the merit of the DOE claim, the majority concluded that substantial evidence supported the Commission's finding of equivalence under the function-way-result framework. This evidence included the following.

With respect to "function," Ajinomoto's expert testified that both E. coli and non-E. coli YddG proteins function as export proteins that actively export aromatic L-amino acids out of the bacterial cell. A 2007 article similarly explains that both proteins are involved in exporting aromatic compounds. And an employee of the accused infringer testified during a deposition that both proteins would be expected to have similar functions based on similarities in the organisms from which they are derived.

As to "way," substantial evidence supported a finding that the two proteins perform the membrane-transport function in substantially the same way, based on the structural similarity of the two proteins, *i.e.*, 85 percent to 95 percent identity in structure.

Finally, as to "result," Ajinomoto's expert testified that, by exporting L-tryptophan out of the bacterial cell, both proteins increase the ability of bacteria to produce and accumulate L-tryptophan. That statement was supported by accused infringer's own fermentation data, which showed that strains containing the E. coli yddG gene but with a stronger promoter, and strains containing the non-E. coli yddG gene with a strong promoter, both showed greater production of L-tryptophan than did strains containing the E. coli yddG gene with the native promoter. In other words, enhancing the expression of either the E. coli or the non-E. coli yddG gene had the effect of increasing production of L-tryptophan, which supports an inference that the proteins encoded by those genes both result in increased L-tryptophan production.

The accused infringer argued that the two proteins do not perform the same function in the same way because the E. coli YddG protein exports aromatic L-amino acids such as L-tryptophan, whereas the non-E. coli YddG protein exports a different compound—namely, paraquat (also known as methyl viologen). But a 2012 article on the record explained that YddG proteins can export both types of compounds, and the court held that the "fact that the non-E. coli YddG protein may be involved in exporting compounds other than L-tryptophan in the non-E. coli organism does not undermine the Commission's well-supported finding that the non-E. coli YddG protein is involved in exporting L-tryptophan in the E. coli bacteria used by [the accused infringer]."

Writing in dissent, Judge Dyk expressed his view that Ajinomoto had not rebutted the presumption of PHE under the tangential relation exception, noting that the Federal Circuit has consistently described this exception as "very narrow." He points out that after the examiner rejected the claim based on prior art disclosing an E. coli protein having an amino acid sequence similar to, but not identical with E. coli YddG, the applicant could have continued to define the scope of the claim in terms of amino acid sequence variations from the E. coli protein, and narrowed the range of permitted variation to exclude the prior art. Instead, however, the applicant deliberately elected to redefine the claimed proteins in terms of the ability of their encoding nucleotide sequences to hybridize with the E. coli yddG sequence as set forth in SEQ ID NO: 1. The amended claim language excluded the prior art because the YfiK encoding DNA sequence disclosed by that prior art did not meet the newly added hybridization requirement. In other words, the anticipating prior art disclosed E. coli YfiK protein, encoded by the yfiK gene, and this prior art was avoided by narrowing the claim to only cover proteins encoded by certain highly similar nucleotide sequences.

Like the prior art asserted during prosecution, the "second later strain" is not literally covered by the amended claims because it is employs a YddG encoding nucleotide sequence that does not hybridize with SEQ ID NO: 1 under stringent conditions. The rationale for the narrowing amendment (avoiding a prior art DNA sequence that does not meet the newly claimed hybridization requirement) directly relates to the accused equivalent (a protein made by an encoding nucleotide sequence that does not meet the hybridization requirement). Judge Dyk would find that the tangential exception cannot apply, because in his view the asserted equivalent is directly related to the reason for the amendment, *i.e.*, to exclude proteins made by an encoding nucleotide sequence that does not hybridize with SEQ ID NO: 1 under stringent conditions.

IV. SOME CONCLUDING THOUGHTS

There was a time when patent practitioners and academic commentators believed that the DOE would play a critical role in supplementing the literal scope of patent claims reciting biomolecules. The *Festo* decisions raised concerns that amendments made during prosecution might one day trigger PHE, and sparked a great deal of discussion amongst patent prosecutors as to claiming and amendment strategies intended to preserve the right of the patentee to successfully assert infringement under the DOE. In retrospect, however, the DOE has come into play relatively infrequently with regard to biomolecule claim limitations, at least as reflected in the decisions of the Federal Circuit. It took until 2019 for the Federal Circuit to issue a decision in which the DOE was successfully asserted in this context, and even then the dissenting judge in *Ajinomoto* would have found the DOE barred by PHE.

Personally, I do not think it was surprising that the majority found infringement under the DOE based on the merits in *Ajinomoto*. The Commission's conclusion that the non-E. coli YddG protein performs substantially the same function in substantially the same way to achieve the same result as the E. coli YddG protein seems well supported by the evidence. *Ajinomoto* is clearly distinguishable over *Genentech v. Wellcome*, in which the accused FE1X protein had a substantially different amino acid sequence and functionality than the human t-PA recited in the claim.

PHE was the more interesting issue in *Ajinomoto*, and this is where the dissent parted from the panel majority. The majority's holding that the tangential relation exception applied does strike me as inconsistent with the Federal Circuit 2006 decision in *Amgen v. Hoechst* (discussed above). The dissent argues persuasively, in light of precedent, that the tangential relation exception should not have been applied, given that the original claim had sought to literally encompass a certain range of amino acid substitutions in the E. coli YddG protein, the claim had been rejected over prior art disclosing an amino acid sequence falling within this range, and the claim had been narrowed to avoid this prior art. The reason for the amendment does not appear to have been tangential to the difference between the recited limitation and the accused product, *i.e.*, variation in the amino acid sequence.

On the other hand, I think that the foreseeability exception could have been found applicable in a case such as this. The Federal Circuit never discusses the foreseeability exception in *Ajinomoto*, presumably because the Commission did not rely on it in its decision. However, given the complexity of the relationship between structure and function in amino acid sequences, and the constraints imposed by the enablement and written description requirements on the ability of patent needs to claim a broadly defined genus of biomolecules, I think a good case could be made that, as a practical matter, it is too much to expect the claim drafter to foresee and literally cover any and all amino acid variations that perform substantially the same function in substantially the same way to achieve the same result. With respect to biomolecule claim limitations in general, it will often be the case that it is unreasonable to expect a patent prosecutor to draft a claim literally encompassing all equivalents, which is the fundamental standard set forth in *Festo II* for overcoming a presumption of PHE.[35]

In retrospect, it is clear that the applicant for the *Ajinomoto* patent did not need to introduce any literal language into the claim expanding the scope of the biomolecule limitation. The finding of infringement under the DOE was based on equivalence between the amino acid sequence of the accused non-E. coli YddG and the amino acid sequence of E. coli YddG protein; the claim language reciting polynucleotides capable of hybridizing under stringent conditions was superfluous. The patentee could have achieved the same result by simply reciting the amino acid sequence of the E. coli YddG protein, and not worrying about literally encompassing variants.

In fact, it seems to me that the only thing that saved the patentee in *Ajinomoto* was that during prosecution, when faced with the prior art rejection, the applicant chose to abandon its initial attempt to achieve scope by claiming variations in the amino acid sequence, and switched over to a limitation reciting polynucleotides capable of hybridizing under stringent conditions to the DNA encoding the amino acid sequence. The more straightforward approach would have been to avoid the prior art by amending the claim in a manner to reduce the scope of variations in the amino acid sequence, *i.e.*, by reciting a smaller number of variations in the amino acid sequence. But if the applicant had done that, it would have been very difficult to successfully argue that the amendment bore only a tangential

[35] 535 U.S. at 741 ("The patentee must show that at the time of the amendment one skilled in the art could not reasonably be expected to have drafted a claim that would have literally encompassed the alleged equivalent.").

relation to the accused equivalent. On the other hand, I think that my comments above regarding the difficulty of foreseeing functional equivalents of amino acid sequences, and the unreasonableness of expecting a claim drafter to literally encompass functional equivalents, would still apply. To me it would not make sense to find the patentee estopped from asserting infringement under the DOE simply because the practitioner who amended the claim chose to switch from amino acid variation to polynucleotide hybridization, rather than the more logical and straightforward approach of amending to claim so as to limit the range of amino acid variation.

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