



**Edward R. Ergenzinger, Jr. and W. Murray Spruill**

Patents on genes and proteins might be severely — even retroactively — affected and lose significant value if the Supreme Court upholds the Appeals Court ruling in the *Festo* case. Applicants seeking patents may be required to make and test thousands of functional variants and describe them all in patent specifications to claim them. The Supreme Court decision is anticipated this summer.

**Edward R. Ergenzinger, Jr.**, is a JD candidate at Wake Forest University and will be joining Alston & Bird, LLP, this fall. Corresponding author **W. Murray Spruill** is chair of the biotechnology patent group at Alston & Bird, LLP, 3201 Beechleaf Court, Suite 600, Raleigh, NC 27604-1062, 919.862.2202, fax 919.862.2260, mspruill@alston.com, www.alston.com.

## Biotechnology Patent Holders Beware!

### A Supreme Court Ruling May Significantly Reduce the Value of Your Patent Portfolio

On 8 January 2002, the Supreme Court heard oral arguments in a case that has been closely watched by patent practitioners: *Festo Corporation v Shoketsu Kinzoku Kogyo Kabushiki Company* (1). *Festo* may significantly limit the application of an equitable doctrine — the doctrine of equivalents (DOE) — that protects patent holders from those who make minor and insubstantial changes to inventions to escape liability from infringement (2,3). The result of a *Festo* limitation is that nearly all 1.2 million unexpired U.S. patents would be narrowed in scope, thus making them harder to assert in court and less valuable when it comes to licensing revenues.

The consequences of limiting the DOE would be more dire for patent holders in biotechnology than most other industries. If biotechnology patentees are not protected against minor and insubstantial changes to their inventions through the DOE, the only way for an applicant to acquire a patent with any value on a gene or protein is to make and test thousands of functional variants, describe them all in the specification, and claim them all. That would unduly burden both applicants and the United States Patent and Trademark Office.

#### The *Festo* Case

*Festo* is on appeal from the Court of Appeals for the Federal Circuit (Federal Circuit), the specialized federal court that has jurisdiction over patent cases. In *Festo*, the Federal Circuit held that patent holders are completely barred from using the DOE for claims that were narrowed during prosecution for reasons pertaining to their patentability (1). Because the traditional approach to patent prosecution was to make broad claims, then limit the claims in response to arguments made by the examiner, *Festo* effectively narrowed the scope of nearly every unexpired patent (4).

The *Festo* decision resulted from the Federal Circuit's dissatisfaction with the indeterminacy that had been created by the DOE as it was understood at the time (5). During the previous 20 years, the Federal Circuit wrestled with how to limit the DOE to prevent it from broadening or expanding the claims of a patent. By asserting a "complete bar" from applying the DOE to claims amended for reasons that are "substantially related to patentability," the court sought to strengthen the notice function of patents (1). In other words, the Federal Circuit wants to provide the public with greater certainty over the scope of patent claims.

The problem with that approach, according to many patent practitioners, is in the meaning of "substantially related to patentability." Before *Festo*, a patentee who narrowed a claim during prosecution was presumably not entitled to later assert that the narrowed claim should be broadened back to its original form (prosecution history estoppel) (6). Patentees could overcome that presumption by showing that the amendment was made voluntarily but only if the narrowing was made for some reason other than to distinguish their invention from other inventions in the public domain or from those described in preexisting patents (prior art) (7).

According to the majority opinion in *Festo*, however, a "substantial reason related to patentability" includes any reason that relates to the statutory requirements for a patent, so the substantial reason is not limited to overcoming or avoiding prior art (1). The idiosyncrasies of biotechnology patent prosecution mean that this new standard could have a disparate impact on patents for biotechnological inventions.

#### The Enablement Requirement

Statutes require patents to describe the claimed invention in enough detail that one of

skill in the relevant technical field would be able to understand how to make or use the invention without undue experimentation (8). That *enablement requirement* poses special problems for biotechnological patent holders.

In patent law, biotechnology is considered an “unpredictable art,” meaning that it is more difficult to predict how a change to a biological invention will affect its function than it is to predict the affect of a change in a mechanical or electrical invention. Because of that unpredictability, patent applications in biotechnology must provide more detail than other technologies to satisfy the enablement requirement (9,10). Inventors who want a patent on nucleotide or amino acid sequences often wish to obtain claims not only to a protein or DNA molecule having one specific sequence, but also to slight and insubstantial modifications. So inventors must decide how many insubstantial modifications to list to satisfy the enablement requirement.

**The Amgen example.** Potential analogs for a protein can be made by substituting interchangeable amino acids at various positions along the length of the protein. As the Federal Circuit observed in *Amgen v Chugai Pharmaceutical Company*, more than 3,600 different analogs of erythropoietin (EPO) can be made by substituting interchangeable acids at only a single amino acid position, and more than a million different analogs can be made by substituting three amino acids (11).

In *Amgen*, the Federal Circuit addressed the application of the enablement requirement to biotechnology patents involving claims relating to analogs of proteins. At issue was a patent for the EPO protein, which is used to stimulate red blood cell production in the treatment of anemia and other blood disorders (11). Amgen owned a patent that claimed all possible DNA sequences coding for analogs of the natural human EPO. The Federal Circuit, although recognizing that “it is not necessary that a patent applicant test all the embodiments of his invention” or even include representative samples at all, nevertheless concluded that the claim was not enabled (11).

The problem with Amgen’s claim to all EPO analogs was that it encompassed an enormous number of possible DNA sequences without any ability to predict the biological activity of their encoded proteins. Although Amgen argued that the 50–80 EPO analogs it

generated were sufficient to show enablement, after five years of experimentation, Amgen could not state whether any of those analogs had the same biological properties as human EPO. Furthermore, the court noted that

This ‘disclosure’ might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen’s desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them. (11)

**Narrowing enablement.** Broad generic claims may still be possible for proteins, but the court provided no guidance on the number of working examples necessary to enable the full range of analogs.

In cases before the Board of Patent Appeals and Interferences (Board), a similar rationale to that used by the *Amgen* court provides further examples. In *ex parte Maizel*, the Board rejected a patent for any DNA sequence encoding a B-cell growth factor (BCGF) protein or “any biologically functional equivalent thereof” (12). The Board found that the claims in question were not enabled because the functional language that was used encompassed “any conceivable means” to achieve the stated biological result, whereas “the specification discloses, at most, only a specific DNA segment known to the inventor” (12). Similarly, *ex parte Ishizaka* involved claims to a nucleic acid sequence that was “effectively homologous” to the disclosed nucleotide sequence (13). The court stated that the claims in question were not enabled because the term “effectively homologous” was defined as “at least 50% homologous to the sequence to be isolated” (13). Using that definition, only nine or 10 nucleotides were required to meet the terms of the claim. The specification had no disclosure showing that a fragment of that size had been effectively employed by the applicant or that it could be employed by others without undue experimentation.

**Multiple embodiments.** All the cases described involved gene and protein enablements that are relatively straightforward because applicants uniformly asserted broad claims but disclosed only one or a few embodiments of the invention (14). More difficult to resolve are cases in which applicants enable multiple embodiments for a broad claim. As described, currently there is a great deal of uncertainty about the

number of working examples that must be provided in a specification to enable a wide breadth of claims for biotechnological inventions. What is certain, however, is that one example is not enough, and that as the unpredictability, complexity, and broadness of an invention increases, the need for more examples also increases (14).

## **Enablement, Festo, and Biotechnology**

Because of the uncertainty regarding the extent to which broad claims for genes and proteins are enabled, such claims are virtually guaranteed to be amended during prosecution in an attempt to address enablement rejections. Unfortunately, even though such amendments are not made to avoid prior art, they would still invoke the “complete bar” under *Festo* and limit the patentee to the exact nucleotide or amino acid sequence claimed. Because “would-be-copyists” can easily make substitutions in the claimed nucleotide or amino acid sequence in ways that retain its biological function, patent holders will therefore be severely prejudiced by a limitation of the DOE.

**The importance of the DOE** for biological patents is not merely a theoretical matter. In another recent case involving Amgen’s EPO (*Amgen, Inc. v Hoechst Marion Roussel, Inc.*), the Massachusetts District Court was called on to assess whether a competitor’s product was infringing Amgen’s patent (15). In *Hoechst*, the case involved Amgen’s patent that claimed EPO as a protein made of 166 amino acids. Hoechst, however, engineered a 165 amino acid variant by deliberately deleting the last amino acid. Although Amgen’s claim was not literally infringed, the court determined that Hoechst’s variant infringed under the DOE.

The *Hoechst* decision confirms that would-be-copyists can easily create analogs by making insubstantial changes to a disclosed sequence. It also illustrates the importance of the DOE in such cases, because Amgen would have lost all the value of its patent (\$1.76 billion in 1999 alone) if it were limited only to asserting literal infringement (15). Unfortunately for many biotechnology patent holders, the prosecution history in question before the *Hoechst* court was unusual because the amendments were not limited in response to a rejection based on the enablement requirement, and so did not invoke the *Festo* complete bar.

In contrast with the *Hoechst* decision, the Federal Circuit in *Mycogen Plant Science, Inc. v Monsanto Company* held that limiting amendments to overcome rejections based on enablement and indefiniteness were sufficient to invoke the *Festo* complete bar and prevent a range of equivalents for the nucleotide sequence (16). Mycogen's application originally claimed a gene that encoded a protein "functionally equivalent" to a naturally occurring protein that was an insecticidal bacterial toxin (Bt). After initial rejection based on the enablement requirement, Mycogen eventually obtained claims directed to a specific disclosed sequence with either a 1,793 or 1,833 nucleotide length (16). The Federal Circuit held that under *Festo*, Mycogen was limited to the literal scope of its claims, allowing competitors to avoid liability by merely changing a single nucleotide out of 1,833 (16).

The prosecution history at issue in *Mycogen* is extremely common among patents that claim nucleotide or amino acid sequences. One alternative for applicants in biotechnology would be to claim narrowly and to provide working examples for every potential functional equivalent to the claimed nucleotide or amino acid sequence. The number of potential analogs or genetic variants makes it too great a burden for applicants to claim every possible equivalent sequence. As stated in an amicus brief filed in *Festo* by Chiron Corporation:

While no doubt a computer could be programmed to print out every analog, the resulting patent claims would be a stack of paper miles high, and would overwhelm the PTO, as well as those who track patents, with their sheer bulk. (17)

### The Effects of *Festo*

If the Supreme Court upholds the *Festo* complete bar, biotechnology applicants will face a Hobson's choice: Describe and claim each nucleotide or amino acid sequence variant, or allow a competitor to design a functional equivalent (17).

**Retroactive effect.** Because there is no "grandfather" provision in the ruling, if the Supreme Court upholds the *Festo* decision, retroactive effects will significantly reduce the value of most of the 1.2 million patents that are unexpired (1). Depending on how the Supreme Court decides *Festo*, valuable property rights could be rescinded from

patentees who relied on the patents to give them a reasonable scope of equivalents (17).

**Effect on patent prosecution.** If *Festo* is upheld by the Supreme Court, biotechnological patent applications could take even longer to acquire because applicants will be increasingly likely to file administrative and judicial appeals (1). If the mere act of amending a claim eliminates all protection under the DOE, then the benefit of pursuing an appeal outweighs its cost. The Board is already backlogged, and "such an increase could result in a significant lengthening in the average time and cost required to prosecute an application to issuance (1)."

**Effect on patent litigation.** Although the rule set forth by the Federal Circuit in *Festo* was an effort to "reign in" the widespread application of the DOE, if *Festo* is upheld, the DOE may apply to most infringement cases, but not for biotechnology. This counter-intuitive effect would arise because future patents will be more likely to contain narrowly drawn claims approved without amendment in the area that affects the allegedly infringing product (1).

Unfortunately for patentees in the biological arts, the persistent uncertainty surrounding the enablement requirement and the inability to list every potential variant of a claimed nucleotide or amino acid sequence will hinder such efforts with respect to most biotechnological patents.

**Effect on licensing.** As mentioned, if *Festo* is upheld, its retroactive effect would significantly and unfairly reduce the value of all unexpired patents that were amended for patentability reasons (1). That decrease would be especially evident to licensees, as noted by Judge Michel of the Federal Circuit Court in his dissenting opinion in *Festo*:

Licensees will be tempted to exploit today's ruling using the method for liability-free copying . . . A licensee could make a minor substitution of a known interchangeable element for an amended claim limitation, and then correctly claim that it is no longer practicing the patented — and licensed — invention. (1)

The Federal Circuit opinion in *Festo* sent shock waves through the patent bar, affecting litigation and licensing for nearly all of the 1.2 million unexpired U.S. patents and spurring immediate changes in prosecution practice. If upheld by the Supreme Court, the *Festo* decision will have a disparate impact on the biotechnology industry. Because of the uncertainty

surrounding the enablement requirement for nucleotide and amino acid sequences, the only way for an applicant to acquire a patent of any value on a gene or protein is to make and test thousands of functional variants, describe them all in the specification, and claim them all. This would unduly burden both applicants and the United States Patent Office.

### References

- (1) *Festo Corporation v Shoketsu Kinzoku Kogyo Kabushiki Company*, 234 F3d 558 (Fed. Cir. 2000), en banc, cert. granted, 121 S. Ct. 2519 (U.S. 18 June 2001), No. 00-1543.
- (2) *Winans v Denmead*, 56 U.S. 330 (1853).
- (3) *Singer Manufacturing Company v Cramer*, 192 U.S. 265, 286 (1904).
- (4) P.F. Fehlnher, "A New 'Biohazard' for Patent Applicants: Broad Biotechnology Claims," *Metropolitan Corporate Counsel* (Insurance Internet Network, March 2001), p. 4.
- (5) *Boehringer Ingelheim Vetmedica, Inc. v Schering-Plough Corporation*, 2001 U.S. Dist. LEXIS 16346 (DC N.J. 21 September 2001).
- (6) *Pharmacia & Upjohn Company v Mylan Pharmaceuticals, Inc.*, 170 F.3d 1373, 1376 (Fed. Cir. 1999).
- (7) *Warner-Jenkinson Company v Hilton Davis Chemical Company*, 520 U.S. 17, 34 (1997).
- (8) *Patentability of Inventions and Grant of Patents: Application for Patent, U.S. Code*, Title 35, Part 11, Sec. 112 (2000).
- (9) *In re Fisher*, 427 F.2d 833, 839 (CCPA 1970).
- (10) R.K. Seide et al., "Drafting Claims for Biotechnology Inventions," *Advanced Claim Drafting and Amendment Writing* 628 PLI/Pat 403 at 449 (Practicing Law Institute Patents Tenth Annual Patent Prosecution Workshop, 2000).
- (11) *Amgen, Inc. v Chugai Pharmaceutical Company*, 927 F.2d 1200, 1212-14 (Fed. Cir. 1991), cert. denied, 502 U.S. 856 (1991).
- (12) *Ex parte Maizel*, 27 USPQ.2d 1662 (Bd. Pat. App. 1992).
- (13) *Ex parte Ishizaka*, 24 USPQ.2d 1621, 1625 (Bd. Pat. App. 1992).
- (14) M. Sampson, "The Evolution of the Enablement and Written Description Requirements Under 35 U.S.C. § 112 in the Area of Biotechnology," *Berkeley Tech.* 15(3), p. 1233, 1248 (2000).
- (15) *Amgen, Inc. v Hoechst Marion Roussel, Inc.*, 126 F.Supp.2d 69 (D.MA 2001).
- (16) *Mycogen Plant Science, Inc. v Monsanto Company*. 261 F.3d 1345, 1349-50 (Fed. Cir. 2001).
- (17) "Brief Amicus Curiae of Chiron Corporation in Support of Petitioner," *Festo Corporation v Shoketsu Kinzoku Kogyo Kabushiki Company*, 234 F3d 558 (Fed. Cir. 2000), en banc, cert. granted, 121 S. Ct. 2519 (U.S. 18 June 2001), No. 00-1543. **BP**