American Intellectual Property Law Association
Biotechnology Committee

Biotechnology in the Courts Subcommittee Report

Summaries of Recent Decisions of Interest to the Biotechnology Community

Prepared for the AIPLA Biotechnology Committee
August 16, 2013

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C O N T R I B U T O R S

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TABLE OF CONTENTS

Case Summaries

I. *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc*., Case No. 2012-1567 - 1570 (Fed. Cir. July 26, 2013)

Reported by: Sung Park

Summary

Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc. is an ANDA (abbreviated new drug application) litigation case revolving around the drug Copaxone, which is used for treatment of multiple sclerosis. Appellants and defendants Sandoz, Inc., Momental Pharmaceuticals, Inc., Mylan, Inc. and Natco Pharma Limited (collectively, "Sandoz") brought this consolidated appeal from the decision of the U.S. District Court for the Southern District of New York.[1] The District Court had held that the defendants failed to prove that the patents-in-suit are invalid for being indefinite, obvious and not enabled, in addition to holding that the defendants' activities infringed upon those patents.

On appeal, the U.S. Court of Appeals for the Federal Circuit upheld the District Court's decision regarding the validity and infringement of Group II claims, but reversed the District Court's decision and held Group I claims invalid for being indefinite. Group I claims claim a range of *average* molecular weight values for copolymer-1 molecules, whereas Group II claims recite the percentage of *actual* molecular weight values that fall within a range. Even though both Group I and Group II claims used the same term "molecular weight", the Court held Group I claims were indefinite because a potential infringer would not be able to ascertain the boundaries of the claims.

Invention

The drug at issue, Copaxone, is used for treatment of multiple sclerosis. Copaxone is a brand name for the active ingredient glatiramer acetate, also known as copolymer-1. Copolymer-1 is a mixture of polymers that are composed of four different amino acids: alanine, glutamic acid, lysine and tyrosine. Eight patents regarding Copaxone are listed in Food and Drug Administration's Orange Book. Teva asserted against the defendants seven of its patents listed in the Orange Book, along with two other patents not listed in the Orange Book.

Background

Teva is the holder of an NDA (New Drug Application) for Copaxone. When the defendants submitted their ANDAs to the Food and Drug Administration for approval of

[1] *See Teva Pharmaceuticals USA, Inc. v. Sandoz Inc.*, 810 F. Supp. 2d 578 (S.D.N.Y. 2011) and *Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc.*, 876 F. Supp. 2d 295 (S.D.N.Y. 2012).

their generic versions of the drug Copaxone, Teva brought patent infringement suits against the defendant companies. The patents-in-suit claim the product copolymer-1 and methods of making the product.

Unlike other chemical compounds, it is difficult to predict the exact molecular weight of polymer molecules. Instead, polymer molecules typically have a distribution of molecular weights values. For example, the molecular weight of one copolymer-1 molecule could differ from that of another copolymer-1 molecule due to different amino acid chain lengths. Accordingly, several statistical measures are used to calculate the average molecular weight values of a given polymer, and these measures oftentimes yield different values for the average molecular weight. Some of these statistical methods are referred to as M_n, M_w and M_p in the present case.

Teva structured its copolymer-1 claims based on the molecular weight values of the polymer molecules by using two approaches. The first approach was to claim a range of *average* molecular weight values for copolymer-1 molecules. It is common to use statistical methods such as M_n, M_w and M_p to calculate the average values. M_p denotes the molecular weight of the most abundant molecule in the sample, and M_n and M_w each represent average molecular weight values that are calculated by using different methods. Most of the times, the values of these three measurements differ from each other. Claims that use this first approach were referred to as Group I claims in this suit. Claim 1 of U.S. 5,981,589, shown below, is an example of Group I claims.

> *Copolymer–1 having a molecular weight of about 5 to 9 kilodaltons, made by a process comprising the steps of:*
>
> > *reacting protected copolymer–1 .; and*
> >
> > *purifying said copolymer–1, to result in copolymer1 having a molecular weight of about 5 to 9 kilodaltons.*

The second approach was to describe what percentage of molecules in a given sample has molecular weights that fall within a defined range. Claims that use this approach were referred to as Group II claims. Claim 1 of U.S. 6,054,430, shown below is an example of Group II claims.

> *Copolymer–1 having over 75% of its mole fraction within the molecular weight range from about 2 kDa to about 20 kDa*

Even though both Group I and II claims use the claim term “molecular weight”, it is important to note that Group I claims refer to the average molecular weight, while Group II claims refer to the actual molecular weight values.

Decision

I. Indefiniteness

In determining whether the term "molecular weight" is indefinite, the Federal Circuit analyzed whether a person of ordinary skill in the art (POSITA) would be able to sufficiently discern the boundaries of the patent claims. Appellants argued that because the term molecular weight is not specifically defined as a value obtained from one of M_n, M_w or M_p methods, and because each of the three terms would result in different scopes of the patent claims, both Group I claims and Group II claims are invalid for indefiniteness. On the other hand, appellee Teva argued that the prosecution history of the patents, together with the usage of Size-Exclusion Chromatography (SEC) method in the specification section as the measurement method, make it clear that the term molecular weight actually refers to M_p values. In addition, Teva argued that Group II claims are not indefinite because Group II claims refer to the exact molecular weight values, not the statistical average molecular weight of the molecules (i.e. M_n, M_w or M_p).

The Court agreed with the appellants' argument that Group I claims are invalid for indefiniteness. However, the Court also accepted Teva's argument that Group II claims should not be invalidated because they refer to the exact molecular weight values.

In particular, regarding the Group I claims, the Court noted that Teva gave two contradictory statements during the prosecution concerning whether the term "molecular weight" refers to M_p or M_w. Furthermore, because both M_w and M_n values, in addition to M_p value, could be calculated from the SEC measurement method described in the patents' specifications, the Court held Group I claims to be indefinite. The term "molecular weight" as used in Group I claims would have been susceptible to multiple interpretations because several statistical methods could be used to calculate the molecular weight of a copolymer-1 molecule.

With respect to Group II claims, the panel focused on the point that Group II claim recite the actual molecular weight values rather than the average molecular weight values of copolymer-1 molecules. A copolymer-1 molecule, regardless of what statistical method is used, has an actual, true molecular weight. Because Group II claims use the actual values not based on statistical calculations, the Court accepted Teva's argument that the claims are not indefinite.

II. Enablement

The parties also litigated the issues of enablement and obviousness. In reviewing the lower court's decision that appellants failed to prove lack of enablement, the Federal Circuit considered whether a POSITA could have calibrated the SEC machine referred to in the patent specifications. Appellants argued that the asserted claims are not enabled because a POSITA could measure the molecular weights by using two calibration methods: self-standards, or universal calibration. The Court affirmed the lower court's decision because there was no clear error in the lower court's determination that a

POSITA could sufficiently make the necessary measurements by using well-known methods at the time.

III. Obviousness

With regard to the issue of obviousness, the Court also rejected the appellants' obviousness argument. The appellants argued that the claimed invention is obvious because the claimed copolymer-1 molecule differs from the previously known copolymer-1 compound only by 1 kDa, and because the claimed invention behaved similarly as the prior art. However, the Court held that there was no clear error in the lower court's analysis which found that prior art teaches away from the claimed invention. The prior art reference, U.S. 3,849,550, disclosed a preferred molecular weight of between 18 – 20 kDa for copolymer-1 molecules, and taught specifically away from lower molecular weight copolymer-1 molecules.

In addition, the District Court had considered in its analysis secondary factors, such as commercial success. The District Court held that "Copaxone is coextensive with the asserted claims", and that therefore, there existed a presumption of a nexus between the drug and the secondary factor (commercial success). The Federal Circuit held that there was no clear error in this part of the analysis.

IV. Infringement

With the patent claims' invalidity issues determined, the Court went on to further review the lower court's infringement analysis. Appellees' US 5,800,808 patent claimed the mixture ratio of "approximately 6:2:5:1" between alanine, glutamic acid, lysine and tyrosine for the copolymer-1 compound. The District Court made its infringement determination by first converting this ratio into percentages (42.9%: 14.3%: 35.7%: 7.1%) and then by seeing whether the accused product's amino acid ratio in aggregate differed by more than 12% from ideal ratio which the Court found equated to the term "approximately 6:2:5:1". Because the products that Sandoz and Mylan produced differed only by 4.5% and 4.4%, respectively, the District Court had held that the '808 patent was infringed. The Federal Circuit affirmed the District Court's decision, stating that no clear error could be found from the lower court's decision.

V. Prosecution History Estoppel

Lastly, the Federal Circuit rejected the appellants' claim that Teva during prosecution disclaimed copolymer-1 compositions that have M_w greater than 10 kDa. Teva had overcome a rejection by differentiating its low molecular weight invention with a prior art copolymer-1 molecule that had a minimum molecular weight of 10 kDa. If the appellants' argument was accepted, this would have meant that copolymer-1 molecules with M_w values greater than 10 kDa could not be claimed by Teva, even if the M_p or M_n value fell within the claimed range. However, because the term "molecular weight" itself is unclear about the method of measurement, the Court held that Teva did not disclaim

the claim scope clearly and unmistakably. Therefore, the Court held that appellants failed to prove that Teva disclaimed compositions with M_w greater than 10 kDa.

Commentary

Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc. shows that claim terms with several possible interpretations can be invalidated for being indefinite. The specification section was unhelpful to Teva because the section did not specify which measurement method was to be used. In addition, prosecution history was actually harmful to Teva and Teva's contradictory statements served as a basis for the Federal Circuit's holding of indefiniteness. These mistakes resulted in Teva's patent term on Copaxone becoming effectively shortened by one year. If a claim term is open to several interpretations, the claim may be held to be indefinite as a potential infringer cannot determine the boundaries of the claims. Therefore, this case highlights the importance of clarifying any possibly ambiguous terms in patent claims and specifications, and the importance of not making contradictory statements during the prosecution stage.

II. *Novozymes A/S v. Dupont Nutrition Biosciences APS*, Case No. 2012-1433 (Fed. Cir. July 22, 2013)

Reported by: Yeu-Yan Perng

Summary

Patent holder Novozymes A/S and Novozymes North America, Inc. (collectively, "Novozymes") appealed from the U.S. District Court for the Western District of Wisconsin's decision to vacate a jury verdict in favor of Novozymes and grant entry of judgment as a matter of law that the claims of U.S. Patent No. 7,713,723 ("the '723 patent") are invalid for lack of adequate written description support required under 35 U.S.C. §112.

The Federal Circuit affirmed in a 2-1 opinion, finding that no reasonable jury could find in favor of Novozymes on the issue of written description requirement because the specification, while setting forth broad parameters for producing and screening candidate alpha-amylase variants, fails to disclose "even a single species that falls within the claims or any 'blaze marks' that would lead an ordinarily skilled [artisan] toward such a species among a slew of competing possibilities." Without such disclosure, the claimed variants cannot be said to have been described. While it may be true that in hindsight, one skilled in the art could find each limitation of the claimed variant in separate sections of the specification, nothing in the disclosure suggests that Novozymes actually possessed the actual functioning, thermostable alpha-amylase variant that those limitations together define.

Background

The '723 patent relates to alpha-amylase variants with increased thermostability relative to a parent alpha-amylase. Specifically, the '723 patent claims alpha-amylase variants from bacteria *Bacillus stearothermophilus* ("BSG" or SEQ ID NO: 6) with a substitution of serine at amino acid sequence position 239, using the amino acid sequence of *Bacillus licheniformis* ("BLA" or SEQ ID NO: 8) for determining position numbering.

The '723 patent issued from a continuation application filed in December 2009 that claimed priority to its original priority patent application filed in November 2000. The specifications of the 2009 continuation application and the 2000 priority application are nearly identical, but Novozymes sought claims drawn specifically to working variants using the BSG alpha-amylase substituted at position 239. Claim 1 is representative:

> 1. An isolated variant of a parent alpha-amylase, wherein:
> (a) the variant has at least 90% sequence identity to SEQ ID NO: 6 [**BSG alpha-amylase**],

(b) the variant comprises **a substitution of serine at position 239** relative to the parent alpha-amylase, using the amino acid sequence of SEQ ID NO: 8 [BLA alpha-amylase] for determining the position numbering, and
(c) the variant has **increased thermostability** relative to the parent alpha-amylase, wherein thermostability is determined at pH 4.5, 90° C and 5 ppm calcium and has alpha-amylase activity.

The specification discloses the sequence of seven potential parent enzymes, including those isolated from BLA and BSG. It also discloses the 33 amino acid positions along the alpha-amylase chain that Novozymes identified as promising mutation targets using rational protein design or random mutagenesis. In addition, the specification indicates that one or more of those sites might be altered in any of the seven disclosed parent alpha-amylases by deletion, addition, or substitution. The specification further indicates that the disclosed variants would exhibit improved stability at high temperatures and provided assays to screen for working thermostable variants.

Defendants-Appellees DuPont Nutrition Biosciences APS, Genencor International Wisconsin, Inc., Danisco US Inc., and Danisco USA Inc. (collectively, "DuPont") and Novozymes are competitors in the market for enzyme preparations. Novozymes brought an infringement suit against DuPont, asserting that one of DuPont's products infringed the '723 patent. DuPont challenged the patent as invalid for failure to comply with the written description requirement. After an eight day trial, the jury returned a verdict that DuPont had not proved by clear and convincing evidence that any of the patent claims at issue failed to comply with the written description requirement. The district court granted DuPont's motion for judgment as a matter of law and held that the claims of the '723 patent were invalid for lack of adequate written description support. The district court vacated the jury verdict and denied all other motions as moot.

Decision

The question before the court was whether the specification "demonstrates to one of ordinary skill in the art that, by the application's filing date, Novozymes had invented the particular alpha-amylase variants that it claimed almost a decade later in the '723 patent." The Federal Circuit found that, while the specification provides textual support for *each individual* limitation recited in the claims of the '723 patent, it does not provide support for the actual functioning, thermostable alpha-amylase variants that those limitations *together* define. The '723 patent claims specific alpha-amylase variants that resulted from mutating a particular parent enzyme at a single amino acid position to yield distinctive function properties, but the specification provides only generalized guidance listing several variables that, in some combination, could lead to a useful result. Such a disclosure that merely sets out multiple possibilities with a desired result is not a written description of the claimed variant, but at best, a roadmap for producing and screening candidate alpha-amylase variants. As such, a person of ordinary skill in the art would not have understood the specification as clearly describing the claimed invention to demonstrate that Novozymes was in possession of the invention. Rather, a skilled artisan reading the specification would have understood that Novozymes had only predicted that

at least some mutations at position 239 would yield variants with increased thermostability, leaving it to the industry to complete an unfinished invention.

The Federal Circuit distinguished the present case from *Union Oil Co. of California v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000), a case heavily relied on by Novozymes in their assertion that a disclosure is not lacking because it relies on the understanding of one skilled in the art. Unlike the recognized level of standardization and predictability of the art of gasoline products in *Union Oil*, even Novozymes' experts agreed that one could not know which, if any, individual substitutions at any of the 33 positions would yield increased thermostability without actually making and testing the variants. Although the specification disclosed the routine assays that one of ordinary skill in the art directed to position 239 would have known to use to test for every possible variant at that position, and thus, would have found the claimed variants as a matter of course, the question is not whether one of ordinary skill in the art presented with the specification would have been enabled to take those final steps, but whether the specification discloses the variants to the skilled artisan as something appellants actually invented.

In conclusion, while the BSG alpha-amylase, amino acid position 239, and improved stability – all recited as limitations in the claims of '723 patent – are *literally* described in the disclosure of the specification, both parties agreed that the specification does not name or exemplify a variant with all the limitations in the claimed variant. The Federal Circuit emphasized that the claims should not be read as a collection of independent limitations such that one could derive written description support from a combination of disclosures working backward from knowledge of the claims. Therefore, the Federal Circuit agreed with the district court that the particular variants claimed in the '723 patent lack meaningful support in the written description of the specification.

In the dissent, Chief Judge Rader emphasized that the written description rule is a question of fact, and concluded that substantial evidence supports the jury verdict in favor of Novozymes, which deserves significant deference. Over an eight-day trial, the jury – in its role as fact finder – "received expert testimony, heard from skilled protein engineers, reviewed visual aids and publication excerpts, and examined the patent document as guided by those skilled in the art." Therefore, he would have reversed the district court's post-verdict grant of judgment and reinstated the jury's verdict.

Commentary

This is one of the most recent cases to explain the written description doctrine after the Federal Circuit *en banc* opinion in *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336 (Fed. Cir. 2010). This is also one of rarer cases that distinguish the enablement doctrine from the written description doctrine in that the specification could enable one skilled in the art to make the claimed invention, but fail to demonstrate possession. *Novozymes v. DuPont* strengthens the fundamental concept that claims will be held invalid in cases where "a patent's written description discloses certain subject matter in terms of a broad genus but its claims specified a particular subgenus or species

contained therein." The fact that the claimed variants are within the *literal* scope of the patent specification in that one skilled in the art can name the claimed variants based on the broad parameters described by the specification does not satisfy as adequate written description. Similar to the holding in *In re Ruschig*, 379 F.2d 990 (CCPA 1967), the "application's undifferentiated description was deficient because it failed to provide sufficient 'blaze marks' to guide a reader through the forest of disclosed possibilities toward the claimed compound, which resided among the myriad of others that also could have been made." Hence, while the degree to which a patent specification must describe the claimed invention to demonstrate possession is still somewhat ambiguous, patent applications should provide working embodiments of the claimed inventions, or at least specify which options are preferred, in order to indicate the applicant's possession of the invention at the time of filing.