



Omeprazole is Over - Or Nearly So¹

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Introduction

Omeprazole is a proton pump inhibitor used to treat peptic ulcers and gastro-esophageal reflux disease (GERD). AstraZeneca received FDA approval to market the drug in the United States, in 1989, as Prilosec®. By 1999, AstraZeneca's product became one of the most widely prescribed drugs of any kind in the world, with sales of some \$6.1 billion annually.²

The AstraZeneca Patents

In 1999 AstraZeneca commenced suit in the United States against four generic pharmaceutical manufacturers³, alleging that the filing of their Abbreviated New Drug Applications infringed as many as eight different patents issued to claimed inventors and assigned to AstraZeneca. Among these patents were U.S. Patent Numbers 4,786,505 and 4,853,230, both of which expired in October 2001. The '505 patent claims, in relevant part,

1. An oral pharmaceutical preparation comprising

(a) a core region comprising an effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound, an alkaline omeprazole salt plus an alkaline reacting compound and an alkaline omeprazole salt alone;

(b) an inert subcoating which is soluble or rapidly disintegrating in water disposed on said core region, said subcoating comprising one or more layers of materials selected from among tablet excipients and polymeric film-forming compounds; and

(c) an outer layer disposed on said subcoating comprising an enteric coating.

The similar '230 patent, subject to a terminal disclaimer, claims:

1. A pharmaceutical preparation comprising:

(a) an alkaline reacting core comprising an acid-labile pharmaceutically active substance and an alkaline reacting compound different from said active substance, an alkaline salt of an acid-labile pharmaceutically active substance, or an alkaline salt of an acid-labile pharmaceutically active substance and an alkaline reacting compound different from said active substance;

(b) an inert subcoating which rapidly dissolves or disintegrates in water disposed on said core region, said subcoating comprising one or more layers comprising materials selected from the group consisting of tablet excipients, film-forming compounds and alkaline compounds; and

(c) an enteric coating layer surrounding said subcoating layer, wherein the subcoating layer isolates the alkaline reacting core from the enteric coating layer such that the stability of the preparation is enhanced.⁴

The Lawsuits

The litigation against the first four generic manufacturers was eventually consolidated, and assigned by the US Judicial Panel on Multi-District Litigation to a single US District Court Judge, in the Southern District of New York. Discovery was commenced. Millions of pages of documents were produced by AstraZeneca, including millions of pages in warehouses overseas. By mid-2000, more than 135 depositions were taken.

In early 2000, four more generic pharmaceutical manufacturers were sued. Included among these "Second Wave" defendants were Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. (together "Mylan"), and its supplier, Esteve Quimica, S .A. and Laboratorios Dr. Esteve, S .A. (together "Esteve").⁵ Mylan filed its ANDA on May 17, 2000 and was sued within 45 days thereafter.

Initially, each of these new, Second Wave defendants was sued in a separate judicial district. After all were served, AstraZeneca moved before the Multi-District Litigation Panel, to consolidate all of these new cases with those already underway in the First Wave. Some of the Second Wave Defendants resisted consolidation, and sought to have their case separately heard in the judicial districts in which AstraZeneca had initially sued them. These Second Wave Defendants opposed consolidation on grounds that, by the time they were sued, fact and expert witness discovery in the earlier consolidated actions was nearly complete, and the most critical hearing in a US patent case, the claim construction or "Markman" hearing, was imminent. These Second Wave Defendants asserted that, by AstraZeneca's motion, they would need to become intimately knowledgeable, almost immediately, about all that had happened in the previously consolidated actions within about six weeks. They asserted that it would be prejudicial to the newcomers to require that they conduct expert discovery, file dispositive motions, and prepare for

the determinative hearing on claim construction in such a short period of time.

AstraZeneca's answer was to have two Waves, and to stay all litigation in the Second Wave, with the exception of limited involvement in claim construction proceedings, until the conclusion of the First Wave trial.

The Judicial Panel on Multi-District Litigation consolidated the Second Wave Defendants with the First Wave, assigning all of the cases to the same US District Court Judge. Although views of the Second Wave Defendants about claim construction were solicited, the balance of the litigation against the Second Wave Defendants was stayed, pending completion of trial of the First Wave cases. Of course, the trial court's claim construction in the First Wave effectively became the "law of the case," and governed the proceedings in the Second Wave.

Trial of most of the First Wave claims occurred before the court, sitting without a jury, on fifty-two trial days between December 6, 2001, and June 13, 2002. On October 16, 2002, more than two years after the litigation against the Second Wave Defendants was commenced, the District Court issued its rulings on the First Wave cases, in a 175 page opinion.⁶ Only Kudco was found not to infringe the '505 and '230 patents.⁷ Andrx and Genpharm, under FDA rules applicable at that time, shared 180-day exclusivity, although both lost to Astra. Both agreed to give up, to the world, their respective rights to 180-day exclusivity, in exchange for a 30 percent share in Kudco's profits, which they split. Kudco was thus enabled to market its 10 mg and 20 mg extended-release omeprazole capsules.⁸ It began to market its generic omeprazole products in December 2002.⁹

Only after the First Wave proceedings concluded, following the trial court's October 2002 opinion, did the proceedings in the Second Wave begin. Once again, millions of pages of documents were produced by AstraZeneca, including transcripts of all of the depositions taken in the First Wave, and the transcript of proceedings in the First Wave trial. Interrogatories were propounded and, after many hearings before a special master appointed by the Court to deal with a plethora of discovery disputes The Second Wave Defendants noted their own depositions¹⁰ and focused their defenses, in light of the claim constructions announced in the October 2002 First Wave trial decision. New expert witnesses were retained by the Second Wave Defendants, to deal with the myriad issues raised by the First Wave opinion, including experts in attenuated total reflectance

Fourier transform infrared spectroscopy ("ATR-FTIR"), ultraviolet fluorescence, energy dispersive x-ray analysis, confocal laser scanning microscopy ("CLSM") and atomic force microscopy. AstraZeneca offered testimony from several experts, as well, continuing to rely principally on one, Dr. Davies, whose laboratory in England, Molecular Profiles, Ltd., conducted the tests whose results were employed by AstraZeneca at trial in their effort to prove infringement.

In the middle of pre-trial proceedings against the Second Wave Defendants, the 30-month stay imposed by the Hatch-Waxman Act expired. On June 2, 2003, the FDA granted final approval to Mylan's ANDA for its 10- and 20-mg. omeprazole products, and tentative approval to its 40-mg. product. Mylan began marketing its 10- and 20-mg. products "at risk," in August 2003.¹¹ AstraZeneca's complaints against Mylan was thereafter amended, to include claims for damages. In June 2003, the US Food & Drug Administration approved AstraZeneca's application to market Prilosec[®], its own omeprazole product, as an over-the-counter product in 20 mg. doses, with three years of market exclusivity for its OTC product.¹²

The Trial Court Decision

On May 31, 2007, following a 42-day long bench trial between April 3 and June 14, 2006, at which the trial court received testimony from 18 expert witnesses, the court entered its opinion on the Second Wave omeprazole cases, consuming some 254 pages.¹³ Mylan's omeprazole products "are oral pharmaceutical preparations in the form of capsules filled with omeprazole-containing pellets," that are "comprised of a sugar seed, a drug layer, two sublayers, and an enteric coating."¹⁴ Although AstraZeneca contended, at trial, that Mylan's formulation infringed the '505 and '230 patents for other reasons rejected by the trial court, the principal dispute arose from AstraZeneca's contention that the "core region," which is prepared by Mylan "by spraying a suspension of [purified water], omeprazole, HPMC, and [micronized] Microace[®] talc onto sugar spheres,"¹⁵ contained an "effective amount of an "alkaline reacting compound,"¹⁶ and, in particular, that "carbonates in Mylan/Esteve's Microace[®] talc and HPMC" were an "ARC" that was present in an "effective amount" in the "core region."¹⁷

The trial court noted that "Talc is a naturally occurring material, which is comprised of purified, hydrated, magnesium silicate," that "[d]ifferent grades or types of talc can have different properties and different pHs," and that

the "Handbook of Pharmaceutical Excipients lists a range of pH values for talc, from an acidic pH of 6.5 to a highly alkaline pH of 10." It noted that "Talc is known to contain materials such as calcium carbonate and magnesium carbonate." Mylan's "specifications for Microace® talc require that it have a pH of not less than 7.0."¹⁸

In an effort to prove that Mylan's talc is an "ARC," despite AstraZeneca's description of talc, in the '505 patent specification, as an "ordinary excipient," rather than an "ARC,"¹⁹ AstraZeneca relied upon ATR-FTIR and energy dispersive x-ray tests performed by Molecular Profiles, under the supervision of Dr. Davies. Dr. Davies testified that the ATR-FTIR tests showed peaks that were "diagnostic of carbonates present within talc," and that the x-ray analysis "indicate[d] that calcium and magnesium are present."

"In contrast to Dr. Davies's results," the trial court said, "both Esteve and the supplier of Microace® talc, Nippon, tested batches of Microace® talc for the presence of carbonates and found no detectable amount of carbonate." The court continued:

This result does not conclusively establish that carbonate is not present, as carbonate could be present in an amount below the level of detection; however, it does suggest that if there is any carbonate present, it is only in very small amounts.

Thus, the Court finds that the empirical evidence of the presence of carbonates in the talc used in Mylan/Esteve's product is inconclusive.²⁰

As suggested above, Mylan prevailed at trial. The court entered a judgment in Mylan's favor, concluding that Mylan's product "does not meet the limitation of claim 1(a)," and "that Plaintiffs have failed to prove by a preponderance of the evidence that Mylan/Esteve infringes, either literally or under the doctrine of equivalents, any of the claim 1 of the '505 and '230 Patents."²¹

The Fed Circuit Decision

AstraZeneca nevertheless appealed. The Court of Appeals for the Federal Circuit heard oral argument on Astra's appeal from the trial court's judgment in Mylan's favor, in mid-May 2008. At the same time, it heard oral argument on the appeals taken by Impax and Apotex from the judgments entered against them. On June 10, 2008, the

Federal Circuit issued its opinion affirming the trial courts' decision in Mylan's favor.

Agreeing with the District Court that AstraZeneca had not met its burden of proving Mylan's infringement of either the '505 or the '230 patents by a preponderance of the evidence, the court noted that "[a]fter weighing the competing evidence, the court found that Astra failed to prove the presence of carbonates in the talc of the accused products." Such a determination, the Court of Appeals said, "is based on the district court's fact findings and cannot be overturned unless we find them to be clearly erroneous, and we do not." *AstraZeneca AB, et al. v. Mylan Laboratories, Inc., et al.*, Slip. Op. at 8.

Curiously, after arguing to the Federal Circuit repeatedly that the District Judge clearly understood the burdens of proof imposed on the litigants in both the First and Second Waves, in its arguments supporting its appeal from the same trial court's ruling in Mylan's favor, AstraZeneca argued that the judgment in Mylan's favor "is flawed because the district court applied the wrong legal standard." According to Astra, the court said, the trial court "misapplied the legal standard by requiring 'conclusive evidence' that carbonates were present in the talc, rather than preponderant evidence." Rejecting these contentions, the Court of Appeals stated that a "plain reading of the district court's decision ... reveals that the district judge knew, understood, and applied the proper standard of proof." Indeed, the Court of Appeals noted, the Second Wave opinion stated:

Plaintiffs bear the burden to prove their claims of infringement by a preponderance of the evidence. A preponderance of the evidence means such evidence which, when considered and compared with that opposed to it, produces a belief that what is sought to be proved is more likely true than not. The fact that section 271(e)(2) creates an artificial act of infringement does not lessen that burden.

Id. Having found no clear error in the district court's decision that AstraZeneca failed to prove that Mylan's products contain non-negligible amounts of carbonates, and that AstraZeneca thus failed to show the presence of an ARC, the Court of Appeals did not address Astra's remaining contentions. It affirmed the trial court's decision. *Id.*

Conclusion

The decision of the Court of Appeals in the *Mylan* case does not represent a major departure from any prior holding. It does not establish any new principle, or set any precedent. It simply ends a case won by Mylan after protracted litigation. Not all Hatch-Waxman litigation, and certainly not all patent litigation, in the United States takes as long to resolve. The lessons, to be learned have more to do with strategy and tactics, or at least endurance, than with any significant legal principles. The costs of litigation for Mylan were undoubtedly great. The legal costs for AstraZeneca were certainly even larger. Nevertheless, for both, the economic rewards were far greater. Almost exactly eight years after AstraZeneca commenced suit against Mylan, and nearly five years after Mylan decided to market its 10- and 20-mg. omeprazole products “at risk,” Mylan’s decision was vindicated by the Court of Appeals and, at least for Mylan, the omeprazole case is over.

The Federal Circuit has yet to rule on the appeals taken by Apotex and Impax. At oral argument, attended by the author, the panel questioned counsel for AstraZeneca and Impax at length about the “public use” of technology described in the ‘505 and ‘230 patents, during the long clinical studies conducted by AstraZeneca. The forthcoming decision of the Court of Appeals, resolving the appeals in the Impax and Apotex cases, will be far more interesting and will likely bring the long history of omeprazole litigation to a final conclusion ... maybe.

Footnotes

¹ By D. Christopher Ohly. The author is a partner in Schiff Hardin, LLP. The views expressed in this article are those of the authors alone and do not necessarily reflect the views of Schiff Hardin, LLP, or any of its past, present or future clients, or those of any other person or party.

² Prilosec sales reached their peak globally in 2000. By 2000, global Prilosec sales were \$6.1 billion, accounting for 35% of all product sales in this drug class. http://www.panopharma.com/world_pharma_sales_2000.htm. Sales remained constant in 2001. http://www.panopharma.com/world_pharma_sales_2001.htm. By 2002, Prilosec sales dropped to \$5.2 billion worldwide, as a result of "competition mentioned above and AstraZeneca's promotion of its follow-up product, Nexium (esomeprazole). http://www.panopharma.com/world_pharma_sales_2002.htm. By 2005, both Prilosec[®] and omeprazole were among the top 100 selling drugs in the United States, with AstraZeneca's follow-on isomeric replacement, Nexium[®], in the top 30. See <http://www.rxlist.com/script/main/art.asp?articlekey=79509>. By 2007, Nexium[®] was the second largest selling drug in the United States, with sales of \$4.355 billion; prescription Prilosec[®] still accounted for another \$174 million in sales (the 171st largest selling product). See <http://www.drugs.com/top200.html>. By 2007, generic omeprazole was the 24th most prescribed drug in the United States, and the 10th largest selling generic pharmaceutical product, with sales of more than \$835 million, a 30% increase over 2006. See <http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard/drugtopics/072008/491181/article.pdf>; and <http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard/drugtopics/102008/500218/article.pdf>.

At their peak, at the beginning of AstraZeneca's litigation against Mylan and the other Second Wave Defendants, global sales of Prilosec were occurring at the rate of \$696,347 *per hour*, 24 hours per day, 365 days per year. At the end of 2001, AstraZeneca reported total sales of \$16 billion and operating profits before extraordinary items, of \$4.1 billion, or approximately 25%. See sec.edgar-online.com/2003/02/07/0000950103-03-000557/Section4.asp. Assuming that the same profit margins were earned on its sales of Prilosec, introduced to market may years earlier, in 2001 AstraZeneca would have had operating profits of \$174,086 *per hour*, every hour of the year. Those operating profits, of course, would have been calculated after deduction of all legal expenses. The army of lawyers employed by AstraZeneca to pursue litigation against generic manufacturers surely cost less than even this amount.

³ The first four generic manufacturers sued were Genpharm, Cheminor, Andrx and Kudco.

⁴ In the context of the '505 and '230 patents, the trial court found that the term "inert subcoating" in both patents required "a coating or covering that is physically on, or in contact with, and conforms to the contours of the core region," that is "substantially continuous," and that is "pharmaceutically, chemically, and pharmacologically inactive." It construed the term "to require that the subcoating be chemically, pharmaceutically, and pharmacologically inactive such that the subcoating does not adversely affect the properties of the active ingredient or the enteric coating material in the formulation," adding that "A person of ordinary skill reviewing the '505 and '230 patent specifications would understand that the invention is a stable formulation. That requires a subcoating that protects the omeprazole and maintains the integrity of the enteric coating. ... The meaning of "inert" flows directly from the invention described in the specification—the subcoating layer cannot adversely affect the properties of the omeprazole or the enteric coating. The patent specification provides that "not adversely affecting . . . the enteric coating" means that the formulation retains gastric acid resistance."

Although some defendants in the First Wave of the Omeprazole litigation argued over the meaning of the term "inert subcoating," none clearly argued to the trial court that the claims of the '230 patent, as written, were not enabled and simply would not work, at least to the extent that they contemplated an "inert subcoating" comprised of "alkaline compounds" (*not* alkaline *reacting* compounds), because such a "subcoating" would react chemically with known "enteric coatings" disposed on such "subcoatings."

The court defined an enteric-coating to be made of a "material is a polymer that is insoluble in acid media *but soluble in neutral to alkaline media*," and that "resists breakdown in the stomach." The court noted that examples of enteric coatings may be found in the '505 patent and "include hydroxypropyl methylcellulose phthalate and Eudragit L-100 brand enteric coating, which is a methacrylic co-polymer." These materials, like other enteric coating materials that are "soluble in . . . alkaline media," would, of course, ordinarily be expected to react in the formulation process, especially a spray coating process that employs water as a solvent, with a subcoating made of "alkaline compounds."

⁵ Also sued in the Second Wave were Apotex Corp., Apotex Inc., and Torpharm Inc. (together "Apotex"), Lek Pharmaceutical and Chemical Company D.D. and Lek USA, Inc. (together "Lek"), Eon Pharmaceuticals ("Eon") and Impax Laboratories, Inc. ("Impax") (collectively "Second Wave Defendants.") Eon, like Lek, was acquired by Sandoz. Eventually, Eon dropped its Paragraph IV claims, and litigation against Eon was terminated. Eventually, AstraZeneca sued other manufacturers in a Third Wave. In April 2008, as part of its settlement with Ranbaxy of Hatch-Waxman litigation over AstraZeneca's esomeprazole product, Nexium[®], AstraZeneca agreed to permit Ranbaxy to market generic omeprazole products in the United States. See *AstraZeneca Settles Ranbaxy Patent Suit*, http://online.wsj.com/article/SB120824391214015579.html?mod=googlenews_wsj.

⁶ *Astra Aktiebolag, et al., v. Andrx Pharmaceuticals, Inc.*, 222 F.Supp. 423 (S.D.N.Y. 2002), *aff'd* 84 Fed.Appx. 76, 2003 WL 22928641 (C.A.F.C. 2003).

⁷ AstraZeneca's claims against Andrx under another patent (US Patent No. 6,013, 281), were resolved against AstraZeneca at a later time. See *Recognizing a Novel Characteristic After the Fact Doesn't Make a Novel Composition New Again*, <http://patentbaristas.com/archives/2007/04/24/recognizing-a-novel-characteristic-after-the-fact-doesnt-make-a-known-composition-new-again/>.

⁸ See *Retail Pharmacy May be Winner in Generic Prilosec Decision*, http://findarticles.com/p/articles/mi_m3374/is_16_24/ai_94673269 (November 18, 2002); and *Commercialization Agreement*, dated October 30, 2002, *Andrx Pharmaceuticals, Inc. 2002 Annual Report*, Ex. 10.67, <http://sec.edgar-online.com/2003/03/31/0000950144-03-004118/Section33.asp>.

⁹ http://www.orangebookblog.com/2006/12/pharmacies_sue_.html

¹⁰ By way of example, the Second Wave Defendants took their own depositions of the inventors named in the '505 and '230 patents, as well as the deposition of a Japanese pharmaceutical librarian (in Tokyo), to whose affidavit - proffered testimony AstraZeneca would not stipulate, and several depositions of AstraZeneca's reticent corporate designee.

¹¹ Lek Pharmaceuticals, also victorious after the Second Wave trial, began marketing its FDA approved 10- and 20-mg. omeprazole products "at risk," on August 19, 2003. AstraZeneca did *not* appeal the trial court's judgment of non-infringement in Lek's favor.

¹² <http://www.fda.gov/bbs/topics/news/2003/NEW00916.html>.

¹³ *In re Omeprazole Patent Litigation*, 490 F.Supp.2d 381 (S.D.N.Y. 2007), *aff'd as to Mylan* No. 2007-1476 (C.A.F.C. June 10, 2008).

¹⁴ *Id.*, 490 F.Supp.2d at 425.

¹⁵ *Id.*

¹⁶ According to the trial court, an "alkaline reacting compound" ("ARC") is '(1) a pharmaceutically acceptable alkaline, or basic, substance having a pH greater than 7 that (2) stabilizes the omeprazole or other acid labile compound by (3) reacting to create a micro-pH of not less than 7 around the particles of omeprazole or other acid labile compound.' *Astra v. Andrx*, 222 F.Supp.2d at 453. The term 'effective amount' 'applies to both omeprazole and the ARC and requires an amount of each substance such that the combination of omeprazole plus the ARC meets the stated goal of the invention of stabilizing the omeprazole.' *id.* at 463." *Id.*, 490 F.Supp.2d at 427 - 28.

¹⁷ As noted above, the '505 patent claimed "An oral pharmaceutical preparation comprising (a) a core region comprising an effective amount of ... omeprazole plus an alkaline reacting compound...; (b) an inert subcoating which is soluble or rapidly disintegrating ... ; and (c) an outer layer ... comprising an enteric coating."

¹⁸ *Id.*, 490 F.Supp.2d at 428 - 29.

¹⁹ *Id.*, 490 F. Supp. 2d at 430. See '505 patent, col.4 ll.54-56, col.5 ll.16-18; '230 patent col.9 ll.48-50, col.10 ll.10-12.

²⁰ *Id.*, 490 F. Supp. 2d at 429 - 30.

²¹ *Id.*, 490 F. Supp. 2d at 447 - 48.

About the Author

D. Christopher Ohly has been a trial lawyer for more than 30 years. A former Assistant U.S. Attorney, Mr. Ohly now concentrates his practice in intellectual property, including Hatch-Waxman generic pharmaceutical litigation, as well as complex business litigation. Mr. Ohly has argued more than 25 cases in federal appellate courts in several judicial circuits, as well as a number of others in state appellate courts, and he has participated in controversies before the U.S. Supreme Court.

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