

BIOTECH BUZZ, June 2012

I. **Eurand, Inc. v. Mylan Pharmaceuticals, Inc., Case No. 2011-1399,-1409 (Fed. Cir. Apr. 16, 2012)**

Reported by: Srikumaran K. Melethil, Ph.D.

Summary

The Court of Appeals for the Federal Circuit (hereinafter “the Federal Circuit”) reversed and vacated the decision of the U.S. District Court for the District of Delaware (hereinafter “the District Court”) that the patents-in-suit were invalid due to obviousness, based exclusively on bioequivalence considerations. The higher court also held that objective considerations were not properly considered by the lower court.

Invention

Plaintiffs Eurand, Inc., Cephalon, Inc., and Anesta, AG (collectively “Cephalon”) are the owners and licensees of US Patent Nos. 7,387,793 (hereinafter the ‘793 patent) and 7,544,372 (hereinafter the ‘372 patent). The ‘793 patent is drawn to a controlled-release dosage form for muscle relaxants, including cyclobenzaprine hydrochloride. The ‘372 patent is drawn to a method for treating muscle spasms using the dosage form described in the ‘793 patent.

Claims of interest (the ‘793 patent):

1. A multi-particulate pharmaceutical dosage form of a skeletal muscle relaxant providing a modified release profile comprising a population of extended release beads,
 - wherein said extended release beads comprise
 - an active-containing core particle comprising a skeletal muscle relaxant selected from the group consisting of cyclobenzaprine, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof; and
 - an extended release coating comprising a water insoluble polymer membrane surrounding said core,
 - wherein said dosage form when dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37 °C exhibits a drug release profile substantially corresponding to the following pattern:
 - after 2 hours, no more than about 40% of the total active is released;
 - after 4 hours, from about 40-65% of the total active is released;
 - after 8 hours, from about 60-85% of the total active is released;
 - wherein said dosage form provides therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful

musculoskeletal conditions when administered to a patient in need thereof; and wherein said water insoluble polymer membrane comprises a water insoluble polymer selected from the group consisting of ethers of cellulose, esters of cellulose, cellulose acetate, ethyl cellulose, polyvinyl acetate, neutral copolymers based on ethylacrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, pH-insensitive ammonium methacrylic acid copolymers, and mixtures thereof; and a plasticizer selected from the group consisting of triacetin, tributyl citrate, triethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil, acetylated mono- and diglycerides and mixtures thereof.

2. The pharmaceutical dosage form of claim 1, wherein said skeletal muscle relaxant comprises cyclobenzaprine hydrochloride.
3. The pharmaceutical dosage form of claim 2 wherein said pharmaceutical dosage form provides a maximum blood plasma concentration (C_{max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCl and an AUC_{0-168} within the range of about 80% to 125% of about 740 ng *hr/mL and a T_{max} within the range of 80% to 125% of about 7 hours following oral administration of a single 30 mg cyclobenzaprine HCl MR Capsule.

Claims of interest (the '372 patent):

1. A method of relieving muscle spasms in a patient in need thereof comprising administering a pharmaceutical dosage form of a skeletal muscle relaxant comprising a population of extended release beads, wherein said extended release beads comprise:
 - an active-containing core particle comprising a skeletal muscle relaxant selected from the group consisting of cyclobenzaprine, pharmaceutically acceptable salts or derivatives thereof and mixtures thereof; and
 - an extended release coating comprising a water insoluble polymer membrane surrounding said core,wherein said dosage form when dissolution tested using United States Pharmacopoeia Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HCl at 37 °C. exhibits a drug release profile substantially corresponding to the following pattern:
 - after 2 hours, no more than about 40% of the total active is released;
 - after 4 hours, from about 40-65% of the total active is released;
 - after 8 hours, from about 60-85% of the total active is released;wherein said dosage form provides a therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions; and wherein said water insoluble polymer membrane comprises a water insoluble polymer selected from the group consisting of ethers of cellulose, esters of cellulose, cellulose acetate, ethyl cellulose, polyvinyl acetate, neutral copolymers based on ethylacrylate and methylmethacrylate, copolymers of acrylic and methacrylic acid esters with quaternary ammonium groups, pH-insensitive ammonio methacrylic acid copolymers, and mixtures thereof; and a plasticizer selected from the group consisting of triacetin, tributyl citrate,

tri-ethyl citrate, acetyl tri-n-butyl citrate, diethyl phthalate, dibutyl sebacate, polyethylene glycol, polypropylene glycol, castor oil, acetylated mono- and diglycerides and mixtures thereof.

2. The method of claim 1, wherein said skeletal muscle relaxant comprises cyclobenzaprine hydrochloride.

3. The method of claim 2 wherein said pharmaceutical dosage form provides a maximum blood plasma concentration (C_{\max}) within the range of about 80% to 125% of about 20 ng/mL of cyclobenzaprine HCl and an AUC_{0-168} within the range of about 80% to 125% of about 740 ng*hr/mL and a T_{\max} within the range of 80% to 125% of about 7 hours following a single oral administration a pharmaceutical dosage form comprising 30 mg of cyclobenzaprine HCl.

Procedural History

The defendants, Mylan Pharmaceuticals, Inc. and Par Pharmaceuticals, Inc. (collectively “Mylan”), filed abbreviated new drug applications (ANDA) for generic versions of a controlled release product containing the active ingredient cyclobenzaprine hydrochloride. The ANDAs included a “Paragraph IV” certification under 21 U.S.C. §355(j)(2)(A)(vii)(IV)(2006) which alleged that the defendants’ generic products would not infringe the patents owned by Cephalon, or alternatively, these patents are invalid or unenforceable. Plaintiff bring an infringement action against the defendant.

Decision

After a bench trial, the District Court found Mylan’s products infringed the patents-in-suit, but also ruled them to be invalid because of obviousness. The District Court ruled that the asserted claims were obvious over prior art immediate-release formulations of cyclobenzaprine. It stated “it would have been obvious to one of skill in the art at the time of the invention to try and create an extended release formulation of cyclobenzaprine mirroring the PK [pharmacokinetic] properties of the immediate release formulation”. (*Op.* at 28). It further went on to state that if the AUC and C_{\max} of the extended release formulation “matches” those of the “already approved immediate release formulation” (*emphasis added*), the immediate and extended release formulation “will have approximately the same effect in the body.” *Id.* In pertinent part for this discussion, Cephalon appealed the invalidity decision.

The Federal Circuit reversed and vacated the District Court’s opinion that the patents-in-suit are invalid for obviousness because it’s opinion was based solely on bioequivalence; objective considerations were not properly considered by the lower court.

Federal Circuit’s Analysis

The introduction (section I) provides a brief summary of the two patents noting that ‘793 is drawn towards an extended-release formulation containing the muscle-relaxant drug cyclobenzaprine (marketed under the name Amrix®, sold by Cephalon) while the ‘362 patent is drawn to a method of treating muscle spasms using this formulation. It provides a “nano” review of extended and immediate release products, and PK/PD (pharmacokinetics/pharmacodynamics).

Next, (section II), the Federal Circuit describes the procedural history and identifies the focus of the appeal, which is the claim limitation “provides [a] therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasms associated with musculoskeletal conditions . . .” *Op.* at 3-4.

The Federal Circuit found that “the District Court’s legal conclusion that bioequivalence alone was sufficient to render the claims at issue obvious was in error” (*Op.* at 9) for the reasons given below:

1. “The district court treated bioequivalence as the end of its inquiry when the court found that it would have been obvious to the person having ordinary skill in the art to target extended-release PK values ‘mirroring’ - in other words, bioequivalent to those of the immediate release cyclobenzaprine formulation.” *Op.* at 10. In this regard, the district should have “consider[ed] the asserted claims’ limitation requiring therapeutic effectiveness, and whether it would have been obvious to one of ordinary skill in the art at the time of the invention that a bioequivalent PK value would satisfy that limitation.” *Id.*
2. Both parties, including their experts, agreed that “cyclobenzaprine lacked a known [PK/PD] relationship”, “skilled artisans could not predict whether any particular PK profile, including a bioequivalent one, would produce a therapeutically effective formulation.”
3. The district court contradicted itself, when it “stated that [t]he lack of PK/PD relationship is of no moment . . . given that one of ordinary skill in the art would expect the extended release formulation to have the same PD effect on the body if it has the immediate release formulation’s PK profile.” *Id.*
4. This contradiction meant “the district court was assuming that a known PK/PD relationship existed for immediate-release formulation.” *Id.*
5. Given the unanimity regarding the lack of a PK/PD relationship for cyclobenzaprine, “there was no way to match the dosage for the extended release formulation, to achieve a known therapeutic effect.”
6. For the reasons above, “[t]he district could not have found obviousness without finding that prior art would have suggested a therapeutic effective formulation to one of ordinary skill in the art.” *Id.*

The Federal Circuit stated that “neither of the [two] prior art references” relied upon by the District Court “supports a finding that the ‘therapeutically effective’ limitation is obvious” (*Op.* at 19).

The Federal Court then addressed the failure of the District Court to properly consider the objective considerations of nonobviousness before arriving at its obviousness decision. By doing so, the Federal Circuit states that the burden of proof was improperly shifted from the defendant challenging the patents to the plaintiff who owns the patents. In this connection, the Federal Circuit admits that “this court has inconsistently articulated the burden of proof applicable to obviousness defense in district court litigation” (*Op.* at 21), because in some instances, “the district court inquires whether the party challenging validity has proven a ‘prima facie’ case of obviousness based on reference to the patent and the proffered prior art, and only then considers objective evidence, asking whether such evidence is sufficient to *overcome* the prima facie case. *Op.* at 24. However, there should be no shifting of burden. It states that the law (*Stratoflex, Inc. v. Aeroquip Corp.*

713, F. 2d, 1530, 1538-39 (Fed. Cir. 1983)) requires ‘that a fact finder consider the objective evidence before reaching an obviousness determination.’ *Op.* at 28.

Finally, the Federal Circuit considers two objective considerations, and concludes that “evidence of a long felt need for an extended-release formulation and the failure of others to formulate one strongly support a conclusion of nonobviousness.” *Op.* at 32. “This court discusses information presented by Cephalon regarding the failure of ALZA Corporation in the 1990s to develop an extended-release cyclobenzaprine formulation, with a dual purpose: therapeutic efficacy and reducing side effects of the drug. ALZA, like Cephalon, used data from the immediate-release product for cyclobenzaprine to develop its extended-release product; however the target concentrations to be achieved by the ALZA product were different from those of Cephalon. Clinical trials had shown that the ALZA product was therapeutically ineffective; at trial, Dr. Saks of ALZA was surprised at this clinical-trial outcome. Though the ALZA and Cephalon products shared the therapeutic effective goal, the District Court had rejected this evidence, because “ in its view, ALZA’s goals were different than Cephalon’s” (*Op.* at 33) The Federal Circuit held that “[t]he district court erred because it disregarded that Cephalon and ALZA did share a central common goal: to create a therapeutically effective product.”

The District Court had rejected Cephalon’s arguments about the long felt need for extended-release cyclobenzaprine, because “Cephalon had failed to offer any expert testimony to support it.” (*Op.* at 36). The Federal Circuit contradicts this by stating “[n]ot only was the district court wrong that Cephalon produced no expert testimony [Dr. David Steiner, a physician testified in support of Cephalon’s extended release product], but the district court was wrong to ignore non-expert evidence proffered on this point.” *Op.* at 37.

Commentary

This decision by the Federal Court of Appeals sets an almost impossible “PK/PD” bar for generic companies to meet, when it comes to challenging existing patents. A PK/PD relationship is a more rigorous embodiment of the therapeutic efficacy principle, where one establishes a mathematical relationship between various concentrations of a drug in the blood and the corresponding effects. Such a relationship is not required for FDA drug approval. Therefore, PK/PD relationships of commercially available drugs are scarce. This agency approves all drugs, both brand and generic, based on two major criteria: safety and effectiveness (Food Drug and Cosmetic Act, Section 505(b)). When a drug is approved for the first time, the innovator is required to produce extensive safety and efficacy data. If a generic version of the same drug is approved by the FDA based on an ANDA submitted by the applicant, bioequivalence data are sufficient to satisfy the safety and efficacy criteria. An ANDA consists primarily of bioequivalence data, consisting of the 3 parameters [for the compared products]: AUC, C_{max} and T_{max} . Therefore, the District Court was correct when it stated that bioequivalent products can be expected to produce similar effects in the body (*supra*, page 6, item 3). In other words, generics are therapeutic equivalents of their brand name counter parts.

Bioequivalence means therapeutic equivalence. A familiar example is the practice of generic substitution in drug therapy, where a cheaper generic bioequivalent is substituted for the more expensive brand name drug, on the well-established belief that the therapeutic efficacy would be the same for both products. Therefore, it would be obvious

for a person with ordinary skill in the art to formulate an extended-release product bioequivalent to the immediate release product.

A clear understanding of the meaning of bioequivalence could have prevented the reversal of the District Court's decision. Bioequivalence is defined as "the absence of a significant difference in the rate and extent rate to which the active ingredient in pharmaceutical equivalents . . . become available at the site of drug action. . . when administered at the same molar dose under similar conditions. Guidance to Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations, FDA 2003, Revision 1, , cited as "the FDA document" in the *Op.* at 18.

FDA considers drug products to be pharmaceutical equivalents if they meet these three criteria "(1) they contain the same active ingredient(s); (2) they are of the same dosage form and route of administration; and (3) they are identical in strength or concentration. Pharmaceutically equivalent drug products may differ in characteristics such as release mechanism"

(<http://www.fda.gov/Drugs/informationondrugs/ucm079436.htm>). Since the specific "site of drug action" for most drugs is unknown, as a practical matter bioequivalence is determined based on the rate and extent to which the drug "becomes available to blood;" AUC, C_{max} and T_{max} are indices of such availability (which the court refers to as "PK" values (*Op* at 4)). Therefore, the Federal Circuit is incorrect when it states that "[t]he document provides little support for an obviousness finding here, because, in the absence of a known PK/PD relationship for cyclobenzaprine, there is no evidence that a skilled artisan would have targeted bioequivalence in the first instance."

As for ALZA's failure to develop a therapeutically effective extended-release product for cyclobenzaprine, it is surprising that ALZA did not follow the widely followed practice of developing an extended release product bioequivalent to the immediate release product. Based on the information provided regarding the choice of the target concentration profile, it appears that ALZA was testing the hypothesis that a "flat-line" concentration profile (typical of zero order release products) between the peaks ("highs") and the troughs ("lows") obtained with immediate release products will be effective.

This hypothesis was proven incorrect by the results of clinical studies. It should also be noted that the Cephalon product was developed about a decade later in relation to ALZA's efforts. During that period, (~ 1990-2000) extended-release technology had progressed significantly, making ALZA's failure less significant. So, the probability of success would have been much higher.

As for the long felt need argument, all extended-release products are developed with the hope of improving patient compliance and are so advertised. Therefore reliability of supportive non-expert opinion should be considered with clear clinical evidence of improved compliance with the extended-release product.

In conclusion, in my opinion, the District Court got it right.

Author BIO.

Srikumaran (“Sri”) K. Melethil, Ph.D. is a registered patent attorney and Of Counsel at Fraser Clemens Martin & Miller in Perrysburg, Ohio. His practice involves patent prosecution, and preparing non-infringement opinions.

Dr. Melethil is Professor Emeritus, Schools of Pharmacy and Medicine, University of Missouri-Kansas City and has published extensively in the areas of pharmacokinetics, bioequivalence drug delivery and analysis, and clinical pharmacology. He has also published articles on Hatch-Waxman litigation, drug doping in sports and FDA regulation of nanopharmaceuticals. He has also served as an expert witness in cases involving drug and chemical toxicity and lethal injection. He is actively involved in educating pharmaceutical scientists about patent law. He serves on the Editorial Boards of Pharmaceutical Patent Analyst, *FDLI Update*, and Clinical Research and Regulatory Affairs. He is a Fellow of the American Association of Pharmaceutical Scientists.

Dr. Melethil obtained his Ph.D. from the Department of Pharmaceutical Sciences, State University at Buffalo, NY, and his J.D. from the University Missouri-Kansas City.