

**DETAILED STATEMENT OF FACTUAL AND LEGAL BASIS FOR
ABRIKA'S OPINION THAT THE '531 PATENT IS INVALID AND WILL NOT BE
INFRINGEMENT**

**I. INTRODUCTION AND SUMMARY OF FACTUAL AND LEGAL BASIS
THAT THE '531 PATENT IS INVALID OR WILL NOT BE INFRINGED**

Sanofi Synthelabo, Inc. ("Sanofi") owns NDA 21-774 for Zolpidem Tartrate extended release tablets, 6.25 mg and 12.5 mg, sold under the brand name Ambien CR™. Ambien CR™ is approved for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance (as measured by wake time after sleep onset). Abrika proposes to manufacture, as set forth in its ANDA specification, zolpidem tartrate extended release tablets containing 6.25 mg and 12.5 mg of zolpidem. Abrika's generic zolpidem tartrate extended release tablets do not infringe the '531 patent listed in the Orange Book with respect to Ambien CR™ and that patent is invalid and unenforceable.

Abrika's product does not infringe the '531 patent. All of the claims of the '531 patent require that "40-70% of the total amount of zolpidem is released during the immediate release phase and the time for release of 90% of the total amount of zolpidem is between 2 and 6 hours." The claim defines the immediate release phase as "having a maximum duration of 30 minutes." Abrika's product does not release 40-70% of the total amount of zolpidem during the immediate release phase as specified in all claims of the '531 patent; on the contrary, it releases significantly more zolpidem during the immediate release phase. Abrika's product therefore does not literally infringe those claims.

Abrika's product also does not infringe under the doctrine of equivalents. The specification of the '531 patent does not disclose any advantages relative to the prior art for choosing the certain percentages of release over the specified time periods. The file history of the '531 patent makes clear that release percentages outside the claimed range of 40-70% have been disclaimed by the Applicant. The patentee inserted the "40-70%" limitation into claim 1 (the only independent claim) as part of a preliminary amendment upon the Examiner's suggestion. The limitation was taken from dependent claim limitations. An Interview Summary and subsequent Notice of Allowability state that the addition of this limitation was the reason for allowance of the patent claims: "the cited references do not fairly teach biphasic controlled release dosage forms comprising zolpidem or a salt thereof over a predetermined time period as disclosed in [revised] generic claim 1." Thus, the patentee of the '531 patent cannot now assert that the patents cover products falling outside of the claimed release time periods.

Furthermore, the claims of the '531 patent are invalid and/or unenforceable under 35 U.S.C. § 103, in view of references that teach biphasic dissolution profiles for short-acting hypnotics and controlled-release formulations for zolpidem.

II. LEGAL STANDARDS FOR INFRINGEMENT

A. Infringement Generally

Under 35 U.S.C. § 271(e)(2), “[i]t shall be an act of infringement to submit—(A) an application under section 505(j) of the Federal Food, Drug, and Cosmetic Act or described in section 505(b)(2) of such Act for a drug claimed in a patent or the use of which is claimed in a patent.” “35 U.S.C. § 271(e)(2)(A) simply provides an ‘artificial’ act of infringement that creates case-or-controversy jurisdiction to enable the resolution of an infringement dispute before the ANDA applicant has actually made or marketed the product. Once jurisdiction is established, however, the substantive determination whether actual infringement or inducement will take place is determined by traditional patent infringement analysis.” *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003).

The patentee has the burden of proving infringement by a preponderance of the evidence. *Warner-Lambert Co. v. Teva Pharms. USA, Inc.*, 418 F.3d 1326, 1341 (Fed. Cir. 2005). Infringement may be literal or under the doctrine of equivalents. In each case the infringement analysis is a two-step process. First, the scope of the claims must be determined. The Supreme Court has held that this first step, sometimes referred to as claim interpretation, is an issue of law exclusively within the province of the court. *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 372 (1996) (“*Markman I*”); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1453 (Fed. Cir. 1998) (en banc). Thus, claim construction necessarily precedes a determination of whether the claims read on an accused product for infringement purposes. *Hormone Research Found., Inc. v. Genentech, Inc.*, 904 F.2d 1558, 1562 (Fed. Cir. 1990); *SmithKline Diagnostics, Inc. v. Helena Labs Corp.*, 859 F.2d 878, 882 (Fed. Cir. 1988).

The second step involves comparing the properly construed claims to the accused product to determine whether those claims “read on” the accused subject matter, i.e., whether all of the claim limitations are present in the accused device, either literally or by a substantial equivalent. *Johnson Worldwide Assocs. Inc. v. Zebco Corp.*, 175 F.3d 985, 988 (Fed. Cir. 1999); *Renishaw PLC v. Marposs Societa per Azioni*, 158 F.3d 1243, 1247 (Fed. Cir. 1998); *Cybor*, 138 F.3d at 1453. This second step is a factual determination and is thus submitted to a jury if the case is not tried to the court. *Markman II*, 517 U.S. at 384 (citing *Winans v. Denmead*, 56 U.S. 330, 338 (1854)).

1. Claim Interpretation

Claim interpretation involves consideration of the language of the patent claim itself, the specification, other claims, the prosecution history, and extrinsic evidence, if necessary. See *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995), *aff’d en banc*, 517 U.S. 370 (1996) (“*Markman I*”). Extrinsic evidence is any evidence that is external to the patent and prosecution history, such as expert testimony, inventor testimony, dictionaries, and technical treatises and articles. *Vitronics*, 90 F.3d at 1584. Finally, “the claims of [a] patent cannot be given a construction broader than the teachings expressed in the patent.” *Studiengesellschaft Kohle GmbH v. Eastman Kodak, Inc.*, 616 F.2d 1315, 1324 (5th Cir. 1980). Thus, the scope of

the claims can be no broader than the scope of the novel invention taught by the patentee in the specification.

The specification should be referred to when construing the limitations of patent claims. Indeed, usually, it is dispositive of the meaning of a term, and has been called "the single best guide to the meaning of a disputed term." *Vitronics*, 90 F.3d at 1582. Thus, the specification may act as a sort of dictionary, which explains the claimed subject matter and may define terms used in the claims. *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1153 (Fed. Cir. 1997); *Markman I*, 52 F.3d at 979. Where the specification contains nothing to indicate that phrases are to be given anything other than their ordinary meanings, then those are the meanings the court must give them. *Enercon GmbH v. Int'l Trade Comm'n*, 151 F.3d 1376, 1384 (Fed. Cir. 1998) (citing *Vitronics*, 90 F.3d at 1582); *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 759 (Fed. Cir. 1984). That is, a technical term used in a patent document is given the same meaning that it would be given by persons experienced in the field of the patent, unless it is apparent from the patent and prosecution history that the patentee used the term with a different meaning. *CVI/Beta Ventures*, 112 F.3d at 1153 (quoting *Hoechst Celanese Corp. v. BP Chems. Ltd.*, 78 F.3d 1575, 1578 (Fed. Cir. 1996)). Thus, "it is always necessary to review the specification to determine whether the inventor has used any terms in a manner inconsistent with their ordinary meaning." *CVI/Beta Ventures*, 112 F.3d at 1153 (quoting *Vitronics*, 90 F.3d at 1582).

2. Literal Infringement

After claim interpretation, a determination is made whether the claims cover the accused products or methods. *Johnson Worldwide Assocs.*, 175 F.3d at 988. In order to infringe a claim, the accused product or method must include every limitation of the claim, either literally or by a substantial equivalent. *Dolly, Inc. v. Spalding & Evenflo Cos.*, 16 F.3d 394, 397 (Fed. Cir. 1994).

To demonstrate literal infringement, a plaintiff must prove that the allegedly infringing product or method embodies every element of the asserted claim(s). *Dolly, Inc.*, 16 F.3d at 397; *Townsend Eng'g Co. v. Hitec Co.*, 829 F.2d 1086, 1090 (Fed. Cir. 1987). This follows from the principle that "[e]ach element contained in a patent claim is deemed material to defining the scope of the patented invention." *Warner-Jenkinson Co., Inc. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 29 (1997); see *Lemelson v. United States*, 752 F.2d 1538, 1551 (Fed. Cir. 1985) (stating it is "well settled that each element of a claim is material and essential"). Thus, "[i]f even one limitation is missing or not met as claimed, there is no literal infringement." *Mas-Hamilton Group v. LaGard, Inc.*, 156 F.3d 1206, 1211 (Fed. Cir. 1998).

3. The Doctrine of Equivalents

Even if a product or process does not literally infringe, there can still be infringement if there is "equivalence" between the elements of the accused product or process and the elements of the patent's claims. *Warner-Jenkinson*, 520 U.S. 17, 21 (1997) (citing *Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 339 U.S. 605, 609 (1950)); *We Care, Inc. v. Ultra-Mark Int'l Corp.*, 930 F.2d 1567, 1571 n.3 (Fed. Cir. 1991). Infringement by equivalents requires that "the accused product or process contain elements identical or equivalent to each claimed element of the patented invention." *Warner-Jenkinson*, 520 U.S. at 40.

To be equivalent, the patentee must prove that the accused product “differs from what is literally claimed only insubstantially, and it performs substantially the same function in substantially the same way to achieve substantially the same result.” *Wright Med. Tech., Inc. v. Osteonics Corp.*, 122 F.3d 1440, 1444 (Fed. Cir. 1997); *Texas Instruments, Inc. v. Cypress Semiconductor Corp.*, 90 F.3d 1558, 1567 (Fed. Cir. 1996); see *Hilton Davis Chem. Co. v. Warner-Jenkinson Co.*, 62 F.3d 1512, 1518 (Fed. Cir. 1995), *rev'd on other grounds*, 520 U.S. 17 (1997) (affirming the viability of the “insubstantial differences” test). The nature of the differences is assessed according to whether a person with ordinary skill in the relevant art would find the differences to be substantial. *Hilton Davis*, 62 F.3d at 1519.

4. Limits on the Doctrine of Equivalents

There are, of course, limitations on the application of the doctrine of equivalents. Both the prior art and prosecution history estoppel limit the range of equivalents. *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1579 (Fed. Cir. 1993), *clarified on other grounds*, 15 F.3d 1076 (Fed. Cir. 1994); *Pennwalt Corp. v. Durand-Wayland, Inc.*, 833 F.2d 931, 934 n.1 (Fed. Cir. 1987) (en banc).

Prosecution history estoppel applies when the applicant surrenders subject matter by either argument or amendment. Arguments, even without amendment, made during prosecution to obtain allowance of the claims at issue give rise to estoppel when such assertions clearly and unmistakably surrender subject matter, even when such arguments were not necessary to distinguish prior art. *Sextant Avionique, S.A. v. Analog Devices, Inc.*, 172 F.3d 817, 828, n.3 (Fed. Cir. 1999) (citing *Hoganas AB v. Dresser Indus., Inc.*, 9 F.3d 948, 952 (Fed. Cir. 1993) and *Texas Instruments Inc. v. United States Int'l Trade Comm'n*, 988 F.2d 1165, 1174-75 (Fed. Cir. 1993)); *Litton Sys., Inc. v. Honeywell, Inc.*, 140 F.3d 1449, 1458 (Fed. Cir. 1998) (citing the same).

During the prosecution of a patent, “a narrowing amendment made to satisfy any requirement of the Patent Act may give rise to an estoppel.” *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 736 (2002). For example, prosecution history estoppel is not limited to amendments made to avoid the prior art, but rather includes amendments made to comply with 35 U.S.C. § 112:

A patentee who narrows a claim as a condition for obtaining a patent disavows his claim to the broader subject matter, whether the amendment was made to avoid the prior art or to comply with § 112. We must regard the patentee as having conceded an inability to claim the broader subject matter or at least as having abandoned his right to appeal a rejection. In either case estoppel may apply.

Id. at 737. Thus, when prosecution history applies, the patentee may only allege literal infringement.

In addition, arguments emphasizing the criticality of a claim element may give rise to a surrender of all competitive products that do not contain the critical element. See *Pharmacia & Upjohn Co. v. Mylan Pharm., Inc.*, 170 F.3d 1373, 1378-79 (Fed. Cir. 1999) (finding all

compositions that do not contain a component described as critical during prosecution and interpreted as indispensable were surrendered during prosecution).

Moreover, there can be no infringement under the doctrine of equivalents if a claim limitation is totally missing from the accused device. *London v. Carson Pirie Scott & Co.*, 946 F.2d 1534, 1539 (Fed. Cir. 1991) (citing *Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 798 (Fed. Cir. 1990)). "The doctrine of equivalents is not a license to ignore claim limitations." *Dolly*, 16 F.3d at 398. That is, a "court cannot convert a multilimitation claim to one with fewer limitations to support a finding of equivalency." *Id.* at 399.

III. LEGAL STANDARDS FOR INVALIDITY

A. The Law of Obviousness Under 35 U.S.C. § 103

For a patent to be valid, the claimed invention must be nonobvious over the prior art to a person having ordinary skill in the art of the invention. Section 103(a) provides in part:

A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

An important consideration is "the need to adhere to the statute, i.e., to hold that an invention would or would not have been obvious, as a whole, when it was made, to a person of 'ordinary skill in the art' – not to the judge, or to a layman, or to those skilled in remote arts, or to geniuses in the art." *Envtl. Designs Ltd., v. Union Oil Co.*, 713 F.2d 693, 697 (Fed. Cir. 1983); *Custom Accessories Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955, 962 (Fed. Cir. 1986).

Several factors guide a court's assessment of obviousness including:

- (1) the scope and content of the prior art;
- (2) the differences between the prior art and the claims at issue;
- (3) the level of the ordinary skill in the art; and
- (4) whatever objective evidence may be present.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966).

When evaluating the scope and content of the prior art, the question under § 103 is not merely what the references expressly teach but what they would have suggested to one of ordinary skill in the art at the time the invention was made. *Merck & Co. Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804, 807 (Fed. Cir. 1989). To invalidate a patent under § 103 using a combination of prior art, there must be some reason, suggestion or motivation found in the prior art whereby a person of ordinary skill would make the combination. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1351 (Fed. Cir. 1998). The motivation to combine can come from the knowledge of those skilled in the art, from the prior art reference itself, or from the nature of the problem to be

solved. *Sibia Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000); *Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996) (holding that such suggestion may “come from the nature of a problem to be solved, leading inventors to look to references relating to possible solutions to that problem”). The ultimate determination of obviousness when evaluating the prior art does not require absolute predictability of success. All that is required is a reasonable expectation of success. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1125 (Fed. Cir. 2000).

Other considerations may be helpful in determining whether an invention is obvious. These secondary considerations include evidence of commercial success, long felt but unsolved needs, failure of others, initial skepticism of experts, praise from experts, copying by an infringer, near simultaneous invention by others, and licenses under the examined patent. *See In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). However, these factors are not considered unless there is a showing of a nexus between the invention and the secondary consideration to ensure that the secondary consideration is not ascribable to other irrelevant factors. *Ryko Mfg. Co. v. Nu-Star Inc.*, 950 F.2d 714, 719 (Fed. Cir. 1991).

Each claim in an issued patent carries an independent presumption of validity. The ultimate question of obviousness is a question of law, which must be supported by clear and convincing evidence. The challenger to the validity of a patent must establish by clear and convincing evidence the facts supporting invalidity. *Ultra-Tex Surfaces v. Hill Bros. Chem. Co.*, 204 F.3d 1360, 1367 (Fed. Cir. 2000). Proof of invalidity is facilitated when prior art not considered during prosecution is material to the issue of validity. *See Stratoflex, Inc.*, 713 F.2d at 1534.

IV. THE '531 PATENT IS NOT INFRINGED AND IS INVALID

A. The '531 Patent Claims, Specification and File History

The '531 patent matured from application serial number 09/857,154, filed on July 16, 2001, which claims priority from PCT Publication No. WO 00/33835, filed December 1, 1999. The '531 patent issued to Alaux et al. on February 4, 2003 and is assigned to Sanofi Synthelabo, Paris. The '531 patent expires on December 1, 2019.

The '531 patent originated as PCT/EP99/10454 filed on December 1, 1999. The International Preliminary Examination Report, completed on 4/18/2001, makes the following observations regarding the applicability of its first reference, D1: EP-A-0 173 928 (AB LEO) 3/12/86, to the claims of the '531 patent: The application is related to a pharmaceutical controlled-release preparation which has a biphasic release profile of active, including a rapid initial release and parameters are directed to be chosen so that a constant, i.e., “zero order release of the active drug in the core is obtained.”

The IPER states that it would be obvious to the skilled person to formulate as claimed in claim 1 of the international application. The IPER states that the inclusion of the maximum duration of 30 minutes and the 40-70% release in the first phase would constitute an inventive step if proved to result in an improved effect or to have overcome shortcomings in using the

biphasic release preparations of reference D1 or D3, but notes that no such evidence is included in the patent application.

Three other references, EP-A-0 361 910, GB-A-2 245 492, and WO 95 20947, were also cited.

To open U.S. prosecution of the application, the applicants made two preliminary amendments on May 31, 2001 and August 28, 2002, respectively. These two amendments changed the claims from those that existed in the international application.

As of the May 31, 2001 Preliminary Amendment, claim 1 stated the following:

1. (Amended) A pharmaceutical controlled-release dosage form adapted to release zolpidem or a salt thereof over a predetermined time period, according to a biphasic *in vitro* profile of dissolution when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia in aqueous buffer at 37°C, where the first phase is an immediate release phase and the second phase is a prolonged release phase.

On August 19, 2002 (an Interview Summary also identifies an interview on September 3, 2002), the Examiner held an interview with the applicants in which, she suggested the incorporation of claims 2, 7, and 8 into generic claims 1 and 9; incorporating claims 2, 7 and 8 into independent claim 1 and amending claim 9 to be dependent on claim 1; thus avoiding the prior art cited. Claims 2, 7 and 8 covered the items excluded from claim 1 of the international application and are emphasized in bold type below. The cited references were U.S. Patent No. 5,629,017 ("programmed release" dosage forms; zolpidem mentioned), U.S. Patent No. 6,309,668 (abuse resistant tablets using gels), U.S. Patent No. 6,372,255 ("biphasic controlled-release dosage form" with multilayer tablet where first layer provides immediate release of an active and the second layer is a matrix providing subsequent release of the same active; zolpidem mentioned), EP 0 173 928 (biphasic pharmaceutical preparation including short-acting hypnotics), EP 0 361 910, and U.S. Patent No. 4,824,678 (claiming a "controlled-release pharmaceutical preparation having a biphasic release profile," and include hypnotics as an active.)

The '531 applicants acquiesced the examiner's suggestion and inserted the limitations from dependent claims 2, 7, and 8 into claim 1 as part of the August, 28, 2002 Supplemental Preliminary Amendment. The result is issued claim 1:

1. A pharmaceutical controlled-release dosage form adapted to release zolpidem or a salt thereof over a predetermined time period, according to a biphasic *in vitro* profile of dissolution when measured in a type II dissolution apparatus according to the U.S. Pharmacopoeia in 0.01M hydrochloric acid buffer at 37° C.
, where the first phase is an immediate release phase **having a maximum duration of 30 minutes** and the second phase is a prolonged release phase, **and wherein 40 to 70% of the total amount of zolpidem is released during the immediate release phase and the time for release of 90% of the total amount of zolpidem [sic] is between 2 and 6 hours.**

On September 6, 2002, the Examiner issued the Notice of Allowance. The examiner's reasons for allowance were that "[t]he cited references do not fairly teach or suggest biphasic controlled release dosage form comprising zolpidem or a salt thereof over a predetermined time period as disclosed in claim 1."

B. Abrika's Proposed Zolpidem Delayed Release Tablet, 6.25 mg and 12.5 mg, Does Not Infringe the '531 Patent

1. Abrika's Proposed Product Does Not Literally Infringe the Only Independent Claim of the '531 Patent

Abrika does not infringe the only independent claim of the '531 patent because the Abrika product does not release the total amount of zolpidem within the 40-70% range specified for the immediate release phase in claim 1 of the '531 patent; on the contrary, it releases more. An infringement analysis begins with interpretation of the patent claims, construed according to their ordinary and customary meaning to a person of ordinary skill in the art. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005). The ordinary meaning is not to be interpreted in a vacuum, but instead should be read in light of the specification and the prosecution history. *Id.* at 1313. One of skill in the art would interpret the 40-70% range by its ordinary meaning, namely 40-70% release within 30 minutes after dissolution begins as specified in the dissolution test. Nothing in the specification or file history alters that plain meaning.

To show literal infringement, the plaintiff must prove that the accused device embodies every limitation of the claim. *Dolly, Inc.*, 16 F.3d at 397. Here, literal infringement is impossible because Abrika's product does not meet the 40-70% limitation. Since the only claim of the '531 patent explicitly requires "40-70% of the total amount of zolpidem is released during the immediate release phase," the Abrika product cannot literally infringe because it releases more than 70% in the immediate release phase.

2. Abrika's Proposed Product Does Not Infringe the Only Independent Claim of the '531 Patent By The Doctrine of Equivalents

Abrika's proposed product does not infringe the only claim of the '531 patent under the doctrine of equivalents. In the absence of literal infringement, infringement still may exist if each limitation of the claim is equivalent to an element of the accused product or process. Equivalence may exist if the element "performs substantially the same function in substantially the same way to obtain the same result." *Graver Tank*, 339 U.S. at 608. During prosecution, the applicants amended claim 1 to include the limitation 40-70% total release in the immediate release phase, the immediate release phase being within the first 30 minutes after initiation of release. By including this limitation, the patentees gave up all other percentages outside the 40-70% range. The patentees cannot argue that the limitation was not made for reasons of patentability, since (1) the amendments were made in specific response to the obviousness determination in the PCT application and the examiner's patentability-related request, and (2) the

examiner expressly stated that part of the reason for allowance was the release over the "predetermined time period disclosed in generic claim 1." Thus, any release outside the 40-70% range within the first 30 minutes after initiation of release was "given-up" by the patentees during prosecution. A presumption of surrender arises if one rewrites dependent claims into independent form. *Honeywell Int'l v. Hamilton Sundstrand Corp.*, 370 F.3d 1131, 1141 (Fed. Cir. 2004). Further, if the patentees wanted the range to be a rough estimate, they would have used a modifier to describe it (e.g., "about" 40-70%); claim 1 includes no such modifiers. Nevertheless, Abrika's product releases significantly more than 40-70% within the first 30 minutes after release. A far-reaching interpretation otherwise would essentially eviscerate the 40-70% claim limitation of claim 1, added during prosecution. Therefore, the doctrine of equivalents is not available to extend the '531 patent claims to encompass the Abrika product.

C. The '531 Patent is Invalid

1. Claim 1 of the '531 Patent is Invalid under 35 U.S.C. § 103

The '531 patent is invalid under 35 U.S.C. §103 because it would be obvious to a person ordinarily skilled in the art to incorporate zolpidem, a short-acting hypnotic, into a controlled-release dosage form to extend the short action of zolpidem over an entire night's sleep. The '531 patent is invalid over the following references:

- (1) European Patent Application EP0173928 to Lindahl et al.
- (2) A.N. Nicholson et al., *Hypnotic activity of an imidazo-pyridine (zolpidem)*¹
- (3) Merlotti et al., "The Dose Effects of Zolpidem on the Sleep of Healthy Normals"²

The Nicholson article and the Merlotti article were not before the Examiner during the prosecution of the '531 patent. Claim 1, the only independent claim of the '531 patent recites:

1. A pharmaceutical controlled-release dosage form adapted to release zolpidem or a salt thereof over a predetermined time period, according to a biphasic in vitro profile of dissolution when measured in a type II dissolution apparatus according to the U.S. Pharmacopoeia in 0.01M hydrochloric acid buffer at 37.degree. C., where the first phase is an immediate release phase having a maximum duration of 30 minutes and the second phase is a prolonged release phase, and wherein 40 to 70% of the total amount of zolpidem is released during the immediate release phase and the time for release of 90% of the total amount of zolpidem is between 2 and 6 hours.

Courts assess obviousness pursuant to §103 by the factors set forth in *Graham*: the scope and content of the prior art; the differences between the prior art and the claims at issue; the level of the ordinary skill in the art; and whatever objective evidence may be present. *Graham*, 383 U.S. at 17 (1966).

¹ A.N. Nicholson & Peta A. Pascoe, *Hypnotic activity of an imidazo-pyridine (zolpidem)*, 21 British Journal of Clinical Pharmacology 205 (1986).

² Lori Merlotti, Timothy Roehrs, Gail Koshorek, Frank Zorick, James Lamphere, and Thomas Roth, *The Dose Effects of Zolpidem on the Sleep of Healthy Normals*, 9(1) Journal of Clinical Psychopharmacology 9 (1989).

Lindahl disclosed an "oral pharmaceutical controlled-release preparation" having "a biphasic release profile." Lindahl. at p. 1, lines 1-3. Particularly, "short-acting hypnotics" are mentioned in the Lindahl application as suitable as a pharmacologically active agent. *Id.* at p. 3, line 33. Lindahl also specifically recites "short-acting hypnotics" in the claims. *Id.* at claim 6. Further, Lindahl disclosed, "[t]he release pattern of the active substance from the tablet core may be adapted to fit various requirement by varying the ratio of pore-creating material versus coating polymer, the combination of pore-creating substances and the coating thickness." *Id.* at p. 3, lines 34-37. See also U.S. Patent 5,629,017, col. 7.

Here, a person ordinarily skilled in the art would be motivated to adapt the dosage form disclosed in Lindahl, with a short-acting hypnotic, in accordance with the teachings of the invention. There must be some reason, suggestion or motivation found in the prior art that motivates the inventor to combine or modify references. *C.R. Bard, Inc.*, 157 F.3d at 1351. Such suggestion or motivation may "come from the nature of a problem to be solved, leading inventors to look to references relating to possible solutions to that problem." *Pro-Mold*, 75 F.3d at 1573. The problem to be solved here is the design of an effective drug formulation for a short-acting hypnotic with a short half-life. According to Nicholson, "[a] drug which is ultra-rapidly eliminated has a very short duration of action and would be ideal for sleep onset insomnia, but to reduce nocturnal awakenings throughout the night a relatively high dose may have to be given."³ Nicholson at 205. In fact, the Merlotti study concluded that, "Zolpidem did not affect sleep maintenance measures."⁴ Merlotti at 13. Merlotti was aimed at finding the "lowest dose of zolpidem that consistently produces hypnotic activity" because "the lowest efficacious dose should be less likely to produce adverse effects." Merlotti at 9. In this case, it would be obvious to employ a controlled release system.

Releasing zolpidem according to the claimed dissolution profile would have been obvious given knowledge of (1) the minimum effective dose of zolpidem; (2) the total amount of active ingredient used in immediate release Ambien®; and (3) the average sleeping time of normal individuals. Ambien® has been available in immediate release 5 mg and 10 mg-strength tablets since 1992. Merlotti discloses that the minimally effective dose of zolpidem was as low as 5.0 and 7.5 mg. Merlotti at 9. A dosage form that released the minimally effective amount (5.0 mg) from a 10 mg-strength tablet would initially release between 40% and 70% the total amount of zolpidem, as required by claim 1. The limitation in claim 1 requiring 90% release between 2 and 6 hours is also obvious. Since one of the goals of a short-acting hypnotic is low incidence next-day side effects,⁵ and assuming that a normal person sleeps between 6 and 8 hours,⁶ it would also be obvious that the dosage form should release 90% of the total amount of active ingredient within a time period that mimics a normal sleep cycle. One skilled in the art

³ Ultra-rapidly eliminated drugs have half-lives between 2 and 3 hours. Nicholson at 205. Zolpidem is rapidly eliminated because it has a mean half-life of 2.4 hours. See Merlotti at 9.

⁴ Sleep maintenance measures, in the Merlotti study, included (1) wake during sleep (2) wake after sleep and (3) number of awakenings. Merlotti at 12. There was no "significant difference from placebo" in the number of awakenings in patients administered 5.0 mg or 10.0 mg doses.

⁵ See Merlotti at 9.

⁶ See Nicholson at 207, Table 1. Total sleep time in minutes with placebo in middle-aged subjects was 439.5 minutes (7.3 hours).

would have the motivation, based on Nicholson, Merlotti and Lindahl, to extend the action of zolpidem longer than its natural half-life, over a full night's sleep, by the dosage form in Lindahl.

In addition, the USP dissolution limitation cannot imbue the claims with patentability. The United States Pharmacopeia is the official standards-setting authority. USP reference standards, such as the dissolution test using a type II apparatus, are required for use in conducting official USP-NF tests and assays. In light of the foregoing, the '531 patent is invalid.

V. CONCLUSION

The marketing of Abrika's proposed zolpidem tartrate delayed release tablet, 6.25 mg and 12.5 mg, in the United States will not infringe any claims of the '531 patent, and all of the claims of the '531 patent are invalid.

Abrika expressly reserves the right to assert additional grounds or defenses relating to non-infringement, invalidity and/or unenforceability of the claims of the '531 patent should such grounds become apparent in the future.