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PATENT & TRADEMARK ATTORNEYS

Undertakings: Intellectual Property Laws, Patents, Trademarks, Designs, Copyrights, Licencing, Investigations, Litigations
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The Controller of Patents
The Patent Office
New Delhi.

Via E-mail / Courier
March 19, 2012

Dear Sir,

Kind Attn: **Dr. Nilanjana Mukherjee**
Asst. Controller of Patents & Designs

Re: Opposition under Section 25(2) against
209251 granted on (Patent application No. IN/PCT/2002/00785/DEL)
dated February 15, 2001
Patentee: Sugen, Inc. and Pharmacia & Upjohn Company
Opponent: Cipla Ltd
Our Ref: **PII/274**

We submit herewith the written notes on arguments on behalf of the opponent in duplicate based on the hearing held on February 21, 2012 in respect of the above case.

The above document may kindly be taken on record.

Yours faithfully,

Ganguli

Dr. Sanchita Ganguli
Of S. Majumdar & Co.
Agent for the Opponent

Encl.: as above

GOVT. OF INDIA PATENT OFFICE
Dy. No. 17723
21 MAR 2012
BAUDHIK SAMPADA BHAWAN
NEW DELHI

BEFORE THE CONTROLLER OF PATENTS, NEW DELHI

In the matter of Section 25(2) of The Patents Act, 1970 *as amended by* The Patents (Amendment) Act 2005;

And

In the matter of The Patents (Second Amendment) Rules 2006

And

IN THE MATTER of Indian Patent No: IN209251 (Patent application No: IN/PCT/2002/00785/DEL) dated February 15, 2001 in the name of Sugen, Inc. of 230 East Grand Avenue, South San Francisco, CA 94080-4811, USA and Pharmacia & Upjohn Company of 301 Henrietta Street, Kalamazoo, MI 49001, USA

…….. Patentee

And

IN THE MATTER of opposition of the grant of a patent thereto by Cipla Ltd, 289 Bellasis Road, Mumbai Central Mumbai 400008, India.

……Opponent

WRITTEN ARGUMENTS OF THE OPPONENT BASED ON THE HEARING HELD ON FEBRUARY 21, 2012 AT PATENT OFFICE, NEW DELHI

As directed by the Ld. Controller, Cipla Limited, being the Opponent in the present opposition proceedings hereby submits written arguments on the submissions made at the hearing in the aforesaid opposition.

The submissions at the hearing were made on the basis of the impugned patent and the pleadings of the parties.

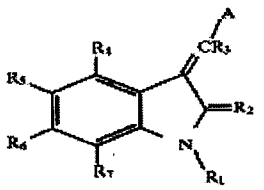
1. The opponent commenced its arguments by stating that the main claim been claim 1 is a Markush and the specific compound Sunitinib is covered in claim 7. The said compound Sunitinib is referred to as compound 80 in the specification. It was submitted that the opponent's arguments will more or less be directed to Sunitinib and reference to other claims / compounds will be made wherever appropriate.
2. Attention of the Ld. Controller was drawn to the assignee, priority and publication dates of the prior art relied upon by the opponent in its written statement (WS).

Document	Assignee	Priority date	Publication date
D1 (US5886020)	Sugen, Inc	June 7, 1995	March 23, 1999
D2 (WO9850356)	Sugen, Inc	May 7, 1997	November 12, 1998
D3 (WO9961422)	Sugen, Inc	May 29, 1998	December 2, 1999.

It was submitted that the aforesaid brings to light the research undertaken in the chain of development of closely related compounds by Sugen (patentee of the impugned patent) and Sunitinib is one amongst the entire plethora of compounds which the patentee has allegedly projected as extraordinary.

3. The opponent submitted that the ground of anticipation has not been taken in its WS which is an implied admission that no single compound discloses the alleged compound of the invention. The ground of obviousness will be substantiated mainly by combination of the teachings of D1 and D3.

4. The attention of the Ld. Controller was drawn to compound of Formula III at column 10 of D1



(III)

wherein the values of substituents when read as R1 – H; R2 = O, R3 = H; R4 = R6 = R7 = H; R5 = Halogen and A = Pyrrole ring such that the pyrrole group is substituted at two positions by alky groups and at one position by –CONRR' wherein R' is alkyl and the definition of an alkyl group includes $N(CH3)_2$ amino (at column 7, line 12 of D1)

5. It was submitted that the compound that is arrived at by making the aforesaid substitutions differs from sunitinib in two aspects viz:

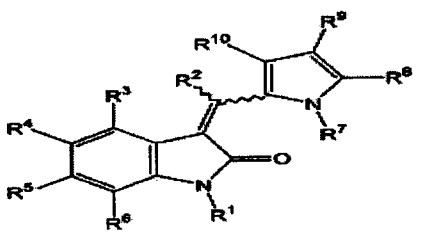
i. the dimethyl group on the terminal amino N atom on the amide group instead of the diethyl group; and

ii. absence of disclosure of the point of the attachment on the pyrrole ring to the doubly bonded carbon connected to the indolinone ring.

It was submitted that the table at paragraph 5.4 at page 11 of the WS, clearly depicts the aforesaid comparison.

6. D3 relates to pyrrole substituted 2-indolinone protein kinase inhibitors. The specific teachings of D3 (which is discussed at paragraph 5.15 at page 17 of the WS) were brought to the attention of the Ld. Controller i.e.

6.1. D3 at page 10 discloses a compound of chemical structure 1 ;



1

Wherein the values of substituents when read as R1 = R2 =R3 = R5 = R6 = R7 = Hydrogen; R4 = Halo (F in sunitinib); R8 = R10 = alkyl (methyl in sunitinib); R9

= (Alk_1) Z; Z is selected from the group consisting of $-C(=O)NR^{13}R^{14}$ wherein R^{13} and R^{14} are independently selected from the group consisting of hydrogen, ..., lower alkyl substituted with a group selected from the group consisting of amino and $-NR^{11}R^{12}$, ..., wherein R^{11} and R^{12} are independently selected from the group consisting of unsubstituted lower alkyl and, ... (at paragraph bridging pages 21 and 22 of D3). It was submitted that though the disclosure of D3 makes the presence of the (Alk1) group essential, there couple of examples of aldehydes which do not fall in the aforesaid definition. Aldehyde is condensed with the oxindole to generate the title compound. The review of the terminal group on the aldehyde will therefore give a clear indication of (Alk1). The specific examples of aldehydes without (Alk1) are *5-formyl-2,4-dimethyl-lH-pyrrole-3carboxylic acid* (line 29, page 27) and *5-formyl-2,4-dimethyl-1Hpyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide* (line 31, page 27).

6.2. In support of the aforesaid, the opponent relied upon the statements made at paragraph 5.20 of the evidence in reply of Mr. D.R. Rao filed under rule 59 wherein it stated that *"I am aware of article namely "Sunitinib: a novel tyrosine kinase inhibitor. A brief review of its therapeutic potential in the treatment of renal carcinoma and gastrointestinal stromal tumors (GIST)" by Christophe Le Tourneau et al (annexed hereto as* ***Exhibit AB****). From the said article it would be apparent SU102662 is a metabolite of Sunitinib and in fact a N-desmethyl metabolite. This clearly indicates that the metabolization is at the N-ethyl position and not at the intervening alkyl position as stated by the applicant and in the Cui affidavit in paragraphs 12-13. Accordingly there was apparently no specific draw-back with the compound of D3 and that formation of a similar compound with a slight modification in structure is but mere trial and error and within purview of a skilled worker. Without prejudice to above even if the skilled worker while trying to develop further compounds might find that the said alkyl position led to easy metabolization and reduced half life of the compound, he would obviously try to overcome the same by removing the alkyl group from position R9 so that the substituent CONR13R14 are directly on the R9 of the pyrrole ring as this would least disturb the known compound of D3 so that the activity is not compromised. I say that even this is mere trial and error within the purview of regular experiment of skilled worker, and in the course if another compound with similar biological activity evolves it cannot be regarded as innovative but mere verification of result so that the known compound with*

known activity is retained with least modification." This disclosure makes it clear that the metabolization occurs at the terminal N atom and not at the position of the (Alk1) group. This defeats the statement of the patentee's expert at paragraph 12 in the evidence files under rule 58 regarding the instability of the compounds of D3 which possess the (Alk1) group.

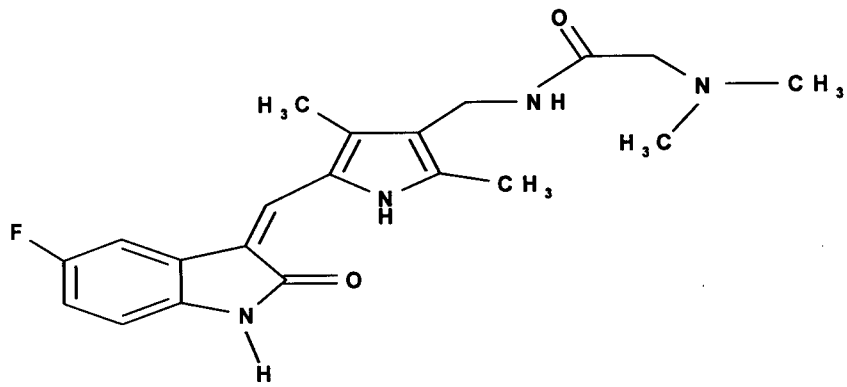
6.3. As regards the rationale for the presence of the polar groups is concerned, it is to be noted that D3 in the paragraph bridging pages 9 and 10, discloses *"while not being bound to any particular theory, applicants at this time believe that the polar groups may interact electronically, for example, but without limitation, through hydrogen bonds, Van der Walls forces and/or ionic bonds (but not covalent bonding), with the amino acids at a PTK active site. These interactions may assist the molecules of this invention to bind to an active site with sufficient tenacity to interfere with or prevent the natural substrate from entering the site. Polar groups may also contribute to the selectivity of the compounds; i. e., One polar group may have greater affinity for a PTK binding domain than other polar groups so that the compound containing the first particular polar group is more potent than the compounds containing the other polar groups."*

6.4. It was submitted that such disclosure makes it obvious for a person skilled in the art to combine the teachings of D1 and D3 to formulate a compound which does not possess the (Alk1) group but retains the protein tyrosine kinase inhibitory activity.

6.5. Attention of the Ld. Controller was drawn to paragraph 2 at page 23 of D3 which discloses the synthesis / combinatorial libraries. At line 6, it is disclosed that *"an additional aspect of this invention is a combinatorial library of at least ten 3-pyrrolidinyl-2-indolinone compounds that can be formed by reacting oxindoles of structure 2 with aldehydes of structure 3."* Amongst the various oxindoles and aldehydes in the combinatorial library, the compounds 5-fluorooxindole (line 10, page 24), 5-formyl-2,4-dimethyl-1Hpyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide lines 31, 32 at page 27 of D3 are disclosed.

6.6. It is noteworthy that the reaction conditions for the synthesis of the compounds of the impugned invention is discussed at page 85 (lines 5 to 15) of the impugned

specification viz *"The appropriately substituted 2-oxindole (1 equiv), the appropriately substituted aldehyde (1.2 equiv) and a base (0. 1 equiv) are mixed in a solvent (1-2 ml/mmol 2-oxindole) and the mixture is then heated for from about 2 to about 12 hours. After cooling, the precipitate that forms is filtered, washed with cold ethanol or ether and vacuum dried to give the solid product. If no precipitate forms, the reaction mixture is concentrated and the residue is triturated with dichloromethane/ether, the resulting solid is collected by filtration and then dried. The product may optionally be further purified by chromatography."* It was submitted that when 5-fluorooxindole (line 10, page 24), 5-formyl-2,4-dimethyl-1Hpyrrole-3-carboxylic acid (2-dimethylaminoethyl) amide are reacted under the conditions specified, a compound of the following structure is obtained;



It is noteworthy that the above compound differs from sunitinib at only the terminal N atom in as much as the former bears a dimethyl group instead of a diethyl group in the latter, Incidentally this compound is compound 132 at page 147 of the impugned patent. *"Example 132 - 5- (5-Fluoro-2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-2, 4dimethyl-lH-pyrrole-3-carboxylic acid (2-dimethylaminoethyl)amide -*

5-Fluoro-1, 3-dihydro-indol-2-one was condensed with 5-formyl-2, 4-dimethyl-lH-pyrrole-3-carboxylic acid (2- dimethylaminoethyl) amide to give the title compound."

6.7. It was further submitted that sunitinib being the homologue of the dimethyl derivative, it is quintessential to compare the activities of these two compounds. However strangely the impugned specification under Table 3 at pages 187 to 190,

gives information of activity till the compound 119 and the activity with respect to the other derivatives contemplated in the impugned patent is not provided.

7. Attention of the Ld. Controller was drawn to the document dated June 8, 2009 which is the affidavit of Dr. Cui, being the reply to the evidence filed by the opponent u/r 59. It was submitted that such evidence was permissible only after seeking leave of the Ld. Controller under rule 60 which procedure has not been followed in the present proceedings. It was further submitted that the submissions of the opponent at the hearing addressed to the issues raised in this subsequent statement be considered as the opponent's replication.

8. Attention of the Ld. Controller was drawn to paragraph 5 of the aforesaid affidavit wherein Dr. Cui has stated that the diethylamine group is present only in the compound of claim 7 and the presence or absence of a diethylamine substituent in the prior art does not render all the claims obvious.

9. Referring to paragraph 26 of the reply statement of the Patentee, it was submitted that merely stating that factual matrix of the Astrazeneca cases and Berwind cases is different from the preset case is denial without reason. It was held in the Astra case that comparison had to be made with the compound bearing maximum structural resemblance. The statements at paragraph 23 stating that – $C(O)NH(CH_2)_2NET_2$ is not disclosed anywhere in D1 and D2, and hence there is no onus on the Patentee to provide any further data is baseless and ought not to be considered. Further Mr. Rao in his affidavit at paragraph 5.5 has categorically pointed out that *"I say that D1 compound the said substitution could be CONRR' as mentioned above R and R' may be hydrogen, alkyl or aryl. The patentee has only referred to the compounds where COOR and methyl groups is present and not to the structure where the said CONRR' is present in the same position. I reiterate my statement at paragraph 5.2 that there is disclosure of alkyls being substituted with diethylamine and amines and alkyls being used interchangeably in D1."* It was submitted that this a deliberate attempt by the patentee to suppress that closely related compounds are disclosed in the prior art. The patentee has conveniently ignored the disclosure of these compounds and thereby avoided furnishing comparative data.

10. Further Mr. Rao at paragraph 5.10, has highlighted that *"I say that the said table has compared compounds of D1, which are not very close to those of the compound in the patent under opposition. I say that the ideal comparison would have been with compound of D1 where at the position of R6 of the compound of the patent under opposition the substitution is CONRR' Vs the compound of the patent under opposition where R6 is C(O)NR'(CH$_2$)$_n$R''. That would have reflected the essence and the effect of the substitution of the alkyl by the amine (diethylamine to be specific). I further say that it is true that substitution of one group with another can cause dramatic change in biological activity. However, if the substitution is known to have similar effect or is known to be interchangeable it becomes obvious to a skilled worker try the same and verify the result."* The aforesaid statements of Mr. Rao make it clear that certain compounds from the prior art were modified by incorporating substituents which were previously disclosed generically and testing such newly formed compounds for their activity. This can be at best treated as verification of results but will certainly be held as an obvious to try exercise especially when the Patentee is active in the said field.
11. When paragraph 6 (c) & (d) of Dr.Cui's affidavit filed with the reply statement are perused, it is evident that a stagewise development starting from the 1990's has happened in this field. It was submitted that this cannot be considered as a path breaking work. It was submitted that when D1 is read with D3, the difference lies in the presence of the diethyl substituent and the absence of the alk1 group in Sunitinib.

12. <u>Case laws relied upon by the Opponent:</u>

12.1. Reasonable expectation of success. D3 teaches two compounds without the (alk1) group. So one will try to experiment such compounds and evaluate their performance. Further the entire prior art literature is attributed to the Patentee itself thereby increasing the probability of experimenting. <u>Pfizer vs Apotex:</u>

Reasonable Expectation of Success

As noted above, the district court found that the skilled artisan would have had no expectation of success in making a besylate salt of amlodipine because there was no reliable way to predict the influence of a particular salt species on the active part of the compound. We cannot reject the district court's finding that in 1986; it was generally unpredictable as to whether a particular salt would form and what its exact properties would be. The problem with the district court's ultimate conclusion of non-obviousness based on that factual finding, however, is that case law is clear that obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success. See In re Corkill, 771 F.2d 1496, 1500 (Fed. Cir. 1985) ("Although [the inventor] declared that it cannot be predicted how any

2006-1261 24 candidate will work in a detergent composition, but that it must be tested, this does not overcome [the prior art's] teaching that hydrated zeolites will work."); see also Brown & Williamson Tobacco Corp. v. Philip Morris Inc., 229 F.3d 1120, 1125 (Fed. Cir. 2000); Merck & Co., Inc. v. Biocraft Labs., Inc., 874 F.2d 804, 809 (Fed. Cir. 1989); In re Merck & Co., Inc., 800 F.2d 1091, 1097 (Fed. Cir. 1986). Indeed, a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt— including those specifically listed in the '909 patent itself—would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute. Merck, 874 F.2d at 809; In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988).

"Obvious-to-Try"

To be sure, "to have a reasonable expectation of success, one must be motivated to do more than merely to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result,

where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) (internal quotations omitted). Pfizer argues that, if anything, amlodipine in its besylate salt form would at most be "obvious to try," i.e., to vary all parameters or try each of numerous possible choices to see if a successful result was obtained. O'Farrell, 853 F.2d at 903.

Parties before this court often complain that holdings of obviousness were based on the impermissible "obvious to try" standard, and this court has accordingly struggled to strike a balance between the seemingly conflicting truisms that, under 35 U.S.C. § 103, "obvious to try" is not the proper standard by which to evaluate obviousness, In re Antonie, 559 F.2d 618, 620 (C.C.P.A. 1977), but that, under O'Farrell and other precedent, absolute predictability of success is not required. 853 F.2d at 903. Reconciling the two is particularly germane to a situation where, as here, a formulation must be tested by routine procedures to verify its expected properties. The question becomes then, when the skilled artisan must test, how far does that need for testing go toward supporting a conclusion of non-obviousness?

As we have said before, "[e]very case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts." In re Jones, 958 F.2d 347, 350 (Fed. Cir. 1992). Consequently, courts cannot decide the obviousness or non-obviousness of a patent claim by proxy. Undue dependence on mechanical application of a few maxims of law, such as "obvious to try," that have no bearing on the facts certainly invites error as decisions on obviousness must be narrowly tailored to the facts of each individual case. As we stated in DyStar,

Obviousness is a complicated subject requiring sophisticated analysis, and no single case lays out all facets of the legal test. [There is] danger inherent in focusing on isolated dicta rather than gleaning the law of a particular area from careful reading of the full text of a group of related

precedents for all they say that is dispositive and for what they hold. When parties . . . do not engage in such careful, candid, and complete legal analysis, much confusion about the law arises and, through time, can be compounded. 464 F.3d at 1367. On the facts of this case, however, we are satisfied that clear and convincing evidence shows that it would have been not merely obvious to try benzene sulphonate, but would have been indeed obvious to make amlodipine besylate.

12.2. Preparation of homologues obvious from prior art disclosure. Disclosure of compound 132 in D3 by way of its process makes compound 80 of the impugned patent obvious. 379 F.2d 1007: Application of Herman Hoeksema:

Para 24 - Appellant's reliance on the *Brown* case is unwarranted. In *Brown,* the invention related to a composition containing a homopolymer of a perfluoroalkyl siloxane and the reference relied on disclosed a composition containing copolymers of a perfluoroalkyl siloxane. We reversed the board's decision in that case because the reference itself stated that "Attempts to prepare fluorine-containing silicone homopolymers have been unsuccessful" thus showing Brown's homopolymers to be not in the possession of the public. There is no comparable showing in the present case. At most, appellant has only demonstrated that *one* method, not here claimed, for making his compound *may* be unobvious and patentable.

Para 26 - In the present case, the Patent Office proceeds upon the proposition that, given a formula and method for producing one compound, a skilled chemist would know how to produce its homolog unless there is something in the record to demonstrate that he would expect some difficulty in doing so. We cannot say that this assessment of the capability of a person skilled in the art is erroneous.

12.3. Reasonable expectation of success. : 800 F.2d 1091; 55 USLW 2236, 231 U.S.P.Q. 375; In re MERCK & CO., Inc; No. 85-2740.

Thus, it appears that the alleged difference in properties between amitriptyline and imipramine is a matter of degree rather than kind. Moreover, as to the sedative effects, the article revealed only a slight difference between the two compounds. Amitriptyline was characterized as "highly sedative" while imipramine was only "somewhat less [sedative] than amitriptyline." Regarding the anticholinergic effect, the article showed that both drugs have anticholinergic effects but to a different degree. These are not truly unexpected results. The Board found in one of its reissue opinions (incorporated in the reexamination decision now on appeal): "[i]n regard to the sedative and anticholinergic properties of amitriptyline, we are not convinced that the side effects of this material [amitriptyline] are significantly or unexpectedly different from the level of those properties exerted by the closest prior art antidepressant, imipramine."

The core of it is that, while there are some differences in degree between the properties of amitriptyline and imipramine, the compounds expectedly have the same type of biological activity. In the absence of evidence to show that the properties of the compounds differed in such an appreciable degree that the difference was really unexpected, we do not think that the Board erred in its determination that appellant's evidence was insufficient to rebut the prima facie case. The fact that amitriptyline and imipramine, respectively, helped some patients and not others does not appear significant. As noted by the Board, a difference in structure, although slight, would have been expected to produce some difference in activity.

12.4. Comparison with the closest prior art. Astra Zeneca vs Natco Pharmaceuticals (Exhibit A of WS)

The closest prior art is defined as a prior art document having maximum structural features in common with the subject-matter of the claimed invention i.e. which requires a minimum of structural modifications in traversing from the prior art to the claimed invention. Thus, the "closest prior art" is determined using a "structural approach" as opposed to a "functional approach", wherein the closest prior art is determined to be the document disclosing most relevant "functional features" in common with the claimed invention.

.....

It was held that only by a comparison with such a prior art could an inference be drawn that at least substantive technical feature of the claimed invention is responsible and origin of the unexpected or surprising advantage over the prior art.

It was submitted that in the present proceedings, the Patentee has chosen a compound which has suited its need and not the compound which has minimum structural difference with the compound 80 of the impugned specification.

12.5. Obviousness of a species when the genus is disclosed. Compounds with structural similarity possess similar properties. 428 F.2d 1341: Application of Paul E. Hoch

Para 21: Having considered, on the one hand, the very close structural similarities of the claimed compounds and the reference compounds, the utility disclosures of the references, and the suggestion of poly-chlorination in the French patent, and, on the other hand, the apparent unobviousness of the utility of the claimed compounds as herbicides, we find that a prima facie case of obviousness has been made out by the examiner.

Para 23: Even if said references sufficed to render obvious the structure of appellant's compounds, they, as a matter of law, would not render obvious the compounds themselves (*and all the properties that inhere therein*)

under 35 USC 103; for the herbicidal utility of these compounds is contraindicated by these references. .....

Para 24: Reflection on this contention shows it to be appellant's position that if his compounds possess an advantageous *property* which is unobvious (unexpected) in view of the disclosures of the prior art references, then the prima facie case of obviousness necessarily has been overcome and his *compounds* must be held to be unobvious. None of the cited cases, however, explicitly or implicitly supports this proposition. In each, a prima facie case of obviousness was conceded or held to have been established and applicant's proofs, submitted to overcome that prima facie case, related not merely to *unexpected* properties, but rather to unexpected *differences* in properties, i. e., to *actual* differences in the properties of the prior art compounds and the properties of the compounds involved in the appealed claims. Such actual differences in properties are required to overcome a prima facie case of obviousness because the prima facie case, at least to a major extent, is based on the expectation that compounds which are very similar in structure will have similar properties. Therefore, to *overcome* the prima facie case, it must be shown that the expectation on which it is based was in fact unsound; *as* by showing that there are substantial, actual differences in properties.

12.6. Obviousness based on structural similarity. 2008 – 1039; Altana vs Teva: Obviousness is ultimately a question of law, based on underlying factual determinations; Richardson-Vicks Inc. v. Upjohn Co., 122 F.3d 1476, 1479 (Fed.Cir.1997). The factual determinations that form the basis of the legal conclusion of obviousness include (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, known as objective indicia of non-obviousness; Graham v. John Deere Co., 383 U.S. 1, 17-18, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). This court recently explained that where, as here, the patent at

issue claims a chemical compound, the analysis of the third Graham factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art, Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1356-57 (Fed.Cir.2008). Thus, to establish a prima facie case of obviousness in cases involving new chemical compounds, the accused infringer must identify some reason that would have led a chemist to modify a known compound in a particular manner. See Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1344 (Fed.Cir.2000). This standard is consistent with the legal principles announced in the Supreme Court's decision in KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007); See Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356 (Fed.Cir.2007); Eisai, 533 F.3d at 1359 (In other words, post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.)

Obviousness based on structural similarity may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound,Eisai, 533 F.3d at 1357. The requisite motivation can come from any number of sources and need not necessarily be explicit in the art, (citing Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed.Cir.2007)). Instead, it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties' to the old (quoting In re Dillon, 919 F.2d 688, 692 (Fed.Cir.1990) (en banc)).

12.7. Problem solution approach. – 357 F.3d 1270: Richard Ruiz and Foundation Anchoring Systems, Inc., Plaintiffs-appellees, v. A.b. Chance Company, Defendant-appellant.

Para 25: This record shows that the district court did not use hindsight in its obviousness analysis, but properly found a motivation to combine because the two references address precisely the same problem of underpinning existing structural foundations. Moreover the record supports the district court's factual finding that Fuller's and Rupiper's work showed that screw anchors worked better than straight push piers. In fact, the evidence shows that Rupiper introduced Chance to the use of screw anchors in underpinning building foundations. Chance then added a metal bracket to the screw anchor.

12.8. A sign post could not be neglected – EPO Board of Appeals – T0154/82:

Para 7: But even if the property of producing hydrogen from water was evidently inherent only in the complexes as claimed, such an additional effect would not have been crucial for the question of obviousness. Apart from that, such an effect, in the Board's view, cannot be incorporated in the definition of a realistic technical problem. The cited article in effect, set a signpost pointing at the carbon capped complexes. This signpost could not be neglected by the skilled man who was engaged with the development of further similar complexes capable of producing hydrogen peroxide, having regard to one facet of the double problem, i.e. the production of hydrogen peroxide.

13. **Not an invention**: It was submitted that this ground is an extension of obviousness and the submissions made with regard to obviousness may kindly be considered relevant to this ground also.

Patentee's Submissions

14. It was submitted that the opponent has not made any submission with respect to D2 or the combination of D2/D3. The Ld. Controller clarified that D2 is not withdrawn and the hearing is conducted mainly for parties to stress upon certain contentions.

15. With regards to D1, it was stated that the pyrrole ring substituent is not disclosed and this document will not render the compounds of the subject patent obvious. With regards to D3, it was argued that one of the substituents from R8, R9 and R10 should essentially bear the (alk1) group. Further it was argued that when Z is $-C(=O)NR^{13}R^{14}$, the term 'combined' has been employed with regard to R^{13} and R^{14}. When such definition is considered, the substitutions do not render Sunitinib obvious. It was further stated that the backbone of the compounds disclosed in the prior art is not the same and the same has to be arrived at.
16. It was also argued that a specific compound will not be rendered obvious by a generic (Markush) prior art disclosure.
17. Referring to Mr. Rao's affidavit, it was argued that compounds 5.101 and 5.100 are not the closest prior art. Compounds provided in Table 1 provided in the reply statement are to be considered as closest prior art. It was emphasized that this patent has been granted in 90 other countries and Sunitinib is the first compound that has been approved for two indications.

Opponent's rebuttal

18. With respect to the contention of the Patentee in respect of substitutions R13 and R14 on the –Z moiety, it is submitted that claim 10 at page 228 of D3 is worded as *"-----R^{13} and R^{14} are independently selected from the group consisting of: ..... And combined, a five-member or a six-member unsubstituted heteroalicyclic, and ....."* From the said claim terminology, it is evident that R13 and R14 may be independently one of the substituents specified or in case they are combined they would be a five or six membered ring. It is submitted that these are two discrete conditions for R13 and R14 and cannot co-exist in any particular compound. The interpretation of the Patentee that the use of the term 'combined' leads to substitutions that are collectively usable and effectively will not render sunitinib obvious are absurd and ought not to be considered.
19. With regards to D1, it was submitted that the Patentee has submitted the structures of compounds 5.100 and 5.101 at the hearing, which makes it clear that the compounds of D1 are indeed pyrrole substituted indolinone compounds. It was

submitted that a disclosure in the description alone will render a impugned compound obvious and need not be necessarily claimed in the prior art to serve as a valid prior art.

20. It was submitted that D2 also discloses pyrrole substituted indolinone compounds and the said fact is evident from paragraph 9 and also table 2 of the Patentee's reply statement.

21. D3 discloses in its abstract that "the present invention relates to novel pyrrole substituted 2-indolinone compounds". Thus D3 is also relevant to the backbone structure and has been misrepresented by the patentee.

22. The opponent categorically brought to the attention of the Ld. Controller that Dr. Cui under oath has stated in his affidavit in support of the reply statement that the IC_{50} of SU11248 (sunitinib) for PDGFRb is 0.01μM (Table 1 at page 62 and Table 2 at page 63). Whereas the impugned specification at page 189, Example 80 indicates that IC_{50} for bio PDGFR is 0.001μM. It was submitted that these values differ by a factor of 10 and the credibility of the expert's statement is questionable.

23. As regards the position of the Patentee that a Markush claim disclosure in the prior art cannot render a claimed compound obvious, it is submitted that claim 7 of the impugned patent is one amongst the various compounds claimed in claim of the impugned patent. In other words one will arrive at the structure of Sunitinib (claim 7) only after attributing specific values to the variants described in the Markush structure.

24. Comments on case laws relied upon the Patentee and that were supplied to the opponent are provided hereinafter:

i. <u>Dr Reddy's Laboratories V Eli lilly & Co Ltd: Court of Appeal EWCA</u>

Referring to the head note and the discussions the applicant in the present case tried to make a case that for rendering obvious the applicant had to choose over a wide range of compound and that the selection of Olanzapine from the teachings of patent'235 was not arbitrary. As regards obviousness over Chakrabarti the Court found that the lower court has not been unreasonable to

find that a person skilled in the art would not have proceeded to test a large number of compounds as suggested by the claimant. The Court further went on to say that there had already been a systematic investigation and that rather than conduct a SAR exercise it would have paid attention to further development of the class if compounds disclosed by Chakrabarti.

The opponent states that this contention does not hold good in the present case. In the present case a huge a lot of compounds do not need to be tested. In fact there is clear mention of on the compound of the impugned invention in the prior art cited. Moreover in the present case there has not been systematic investigation unlike the case law cited. Hence a person skilled in the art would look for SAR exercise and reach the impugned compound. More so since the prior art belongs to the same patentee. In fact the Expert Cui has mention about SAR activity being the involved in D1 to D3. This case law is not relevant for the present case.

ii. Ruiz V AB Chance- US Court of Appeals, Federal Circuit

In this case the court found non obviousness and continued that there was a great deal of evidence presented before the district court that the applicant's method represented improvement over the prior art. According to the Court of Appeals the District it is not clear whether the District Court evaluated the evidence in its obviousness analysis.

The opponent states that in the present case the patentee failed to provide any comparative data with the closest prior art which is requirement to establish inventive step. There is no evidence to show superior properties in the present case. Based on evidences the case in the cited decision had been considered favourable for the applicants. No such evidence/ comparative data has been put forward by the patentee in the present case to demonstrate superior property even though requirement of the same was mentioned the representation itself. Thus this case is also irrelevant for the present matters for considering obviousness issue.

iii. Daiichi Sankyo V Matrix Laboratories, US Court of Appeals, Federal Circuit.

The patentee mainly contended on the selection of the lead compound.

The opponent states that the case law teaches that the applicant would not have selected certain compound as the lead compound in the light of other more favourable compounds. In the present case there are no mention of any specific compounds which have more favourable properties and nor the same has been pointed out by the applicant. The opponent has shown compounds of D1 to D3 to be structurally close and thus the structurally closest was available to the applicant to choose as the lead compound. There is no data that the other compounds with less similarity had closer properties so that the person skilled in the art would be dissuaded to follow the said lead compound and use the other more promising compound. Thus this case law favors the opponent rather the applicant. The lead compound should have most structural similarity which the opponent has already shown and that there is no compound has properties similar to those of the impugned invention than the lead compounds. Thus the impugned invention is obvious.

iv. Takeda Chemical Industries V Alpha Pharm pty Ltd US Court of Appeals, Federal Circuit

In this case the court found non obviousness as the lead compound could not be found from the many compounds disclosed in the prior art and also it could not be ascertained as to which would possess the property as to non toxicity or absence of side effects in such compounds which are properties of the compounds of the said invention so that they can be engaged for increasing efficacy.

In the present case this is not applicable as there is no increase in efficacy and no feature which is shown to be different from the compounds for the prior art. Rather all the compounds of the prior art are for the same purpose and the applicant has failed to give any data on the comparative test with prior art compounds. Thus the choice of the lead compound in the present case is distinct and that the compounds of D1 and D3 do act as lead compound and there is no data to show any particular property which is not found in the said lead compounds or the property being better than lead compound. Hence this

case is not applicable to the present situation and the application is rendered obvious.

v. Non Drip Measure Coy v Stranger's Ltd And Others- In the House of Lords

In this case the invention was held inventive as it was shown that in the device of the invention there was new and valuable results achieved by inverting an existing device. There is completely different disposition of the components parts which achieved desired result.

Drawing analogy to the present case, there is no such step which has been taken from the compounds of the prior art so that an improvement is achieved. Hence this case is irrelevant for the present proceeding and does not support inventive step.

vi. 1032/MAS/1997- Hoffmann La Roche V Wockhardt & Sankalp Rehabilitation Trust

The opponent has vehemently opposed putting forward this case as this is under Appeal at the IPAB. Hence this ought not to be considered. Without prejudice to the same it is stated that the teachings of the said case are also different. There is no data / comparative data in the present case to support inventive step

vii. Bishwanath Prasad Radhey Shyam V Hindustan Metal Industries.

It is not clear why this case was cited by the applicant. It clearly says that it needs to be seen whether the invention is so much out of the track of what is known before as not naturally to suggest itself to a person skilled in the art. In the present case the compound of the impugned invention is envisaged in the prior art and there is nothing out of the track as the same is also used for the purpose as taught in prior art. Thus the impugned invention is obvious

viii. Press Metal Corporation Ltd V Noshir Sorabji Pochkhanwalla and Anr.

It is not clear why this case was cited by the applicant. It clearly that it was obvious and lacked inventive step and that it was no more workshop modification. This thus helps the opponent rather than the applicant.

ix. Excerpt from Patent law by Narayanan – Second Edition

It is not very clear why the applicant has cited this portion. It is known that inventive step and novelty are not one and the same. The opponent did not take the ground of lack of novelty but lack of inventive step was argued. Further paragraph 1044 at page 103 clearly mentions that "it *is a disclosure of a fact, and even if no chemist could have appreciated that it was right, if it turns out that it is right, you cannot takeout patent for verifying a prior statement*"

The opponent states that this is exactly what the opponent has tried to argue that even if no chemist found the specific compound from D1 and D3 to also work in the manner the others did, the fact that it did only amounted to verification of result and no patent can be granted for the same.

The opponents reiterate that the impugned patent is obvious and lacks inventive step

25. In view of the above the patent application may be revoked in toto as it is in breach of the various provisions of the Act as placed before the Ld. Controller with the written statement as well as at the hearing.

Dated this the 19th day of March, 2012

Dr. Sanchita Ganguli
(OF S.MAJUMDAR & CO)
Opponents' Agent.