* **IN THE HIGH COURT OF DELHI AT NEW DELHI**

% Decided on: 30th January, 2020

\+ **CS(COMM) 27/2020**

BRISTOL-MYERS SQUIBB HOLDINGS IRELAND UNLIMITED COMPANY & ORS. ..... Plaintiff

Represented by: Mr. Pravin Anand, Ms. Archana Shankar, Ms. Tusha Malhotra, Ms. Prachi Agarwal, Ms. Ridhie Bajaj, Mr. Devinder Rawat, Ms. M. Dubey, Advs.

versus

BDR PHARMACEUTICALS INTERNATIONAL PVT. LTD. & ANR. ..... Defendant

Represented by: Mr. J. Sai Deepak, Mr. Avinash K. Sharma, Mr. Abhishek, Advs.

CORAM:
HON'BLE MS. JUSTICE MUKTA GUPTA

MUKTA GUPTA, J. (ORAL)

I.A. 803/2020 (u/O XXXIX R 1&2 CPC)

1. The present suit and application came up before this Court on 21st January, 2020 when learned counsel for the defendants urged that he had additional material to oppose the ad-interim injunction de-hors what was argued in the earlier round of litigations between the plaintiffs and third parties wherein this Court had granted ad-interim injunction against which appeals are pending before the Hon'ble Division Bench.

2. Part arguments were addressed on behalf of the parties on 21st January, 2020 whereafter the hearing was kept at end of the board on 22nd January, 2020 and learned counsel for the defendant handed over nine

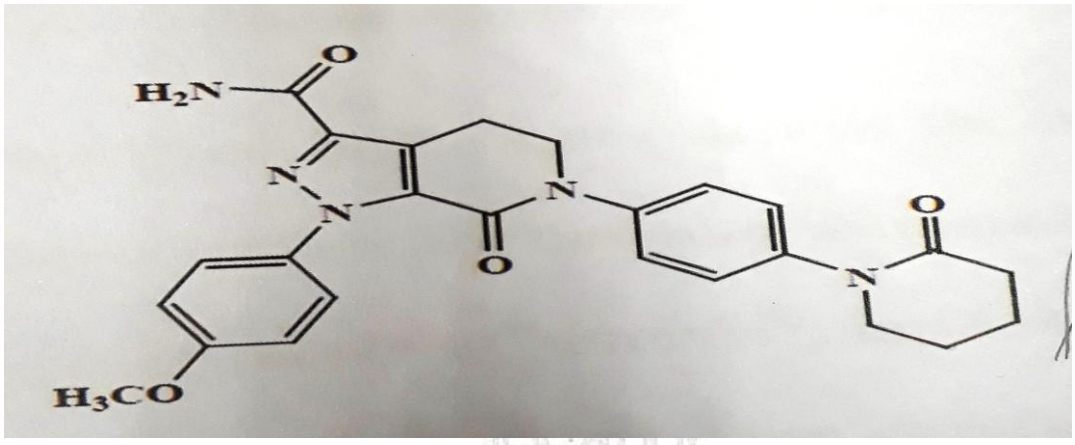
documents including a revocation petition filed in December, 2019 on which he would base his arguments to the Court and learned counsel for the plaintiffs. In the post-lunch session on 22nd January, 2020 learned counsel for the defendant was on his legs in the Hon'ble Supreme Court when this Court directed learned counsel for the plaintiff to address arguments on the 9 documents relied upon by the defendant. Thereafter, arguments were heard and concluded on behalf of learned counsel for the defendant on 23rd January, 2020 and only for rebuttal by the plaintiff's counsel to the extent additional material used by the defendant, the matter was kept on 27th January, 2020.

3. Case of the plaintiffs is that plaintiff No.1 is a company incorporated under the laws of Ireland whereas plaintiff Nos.2 and 3 are companies incorporated under the Companies Act, 1956 in India. Plaintiff No.1 is the owner of the suit patent titled as "Lactam-Containing Compounds and Derivatives Thereof as Factor Xa Inhibitors" and has been granted the Indian Patent No.247381 (in short 'IN-381') pursuant to an application filed in India on 9th March, 2004. The date of grant of the patent is 4th April, 2011 and the date of publication is 8th April, 2011. The suit patent would expire on 17th September, 2022. As per the plaintiff US Patent 6967208 is equivalent to the suit Patent IN-381.

4. Plaintiffs' claim is that the suit patent has not been subjected to any pre-grant or post-grant opposition in India except by one i.e. NATCO Pharma Limited which filed a petition seeking revocation of the suit patent on 9th May, 2016 which is currently pending before the appellate board and the one now stated to be filed by the defendant in December, 2019.

5. The suit patent specifically describes and covers a molecule having an

International Non-Proprietary Name (INN) APIXABAN and the IUPAC name 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl) phenyl]-4,5,6, 7-tetrahydro-1H-pyrazolo[3,4-c] pyridine-3-carboxamide. It is used for the prevention and treatment of thromboembolic diseases. The molecular formula of APIXABAN is $C_{25}H_{25}N_5O_4$. APIXABAN has the following structural formula:



6. Claim of the plaintiffs is that APIXABAN addresses many limitations of the problems associated with the prior standard of care for the treatment of thrombosis with an oral anticoagulant (i.e. warfarin) by: (i) reducing bleeding without compromising efficacy and (ii) dramatically reducing drug-drug interactions with other therapeutic agents, which makes APIXABAN suitable for concurrent administration with other drug products.

7. Prior to the suit patent IN-381 the plaintiff No.1 had been granted Indian Patent No.243917 for 'Nitrogen Containing Heterobicycles As Factor Xa Inhibitors'. On 11th November, 2010 the plaintiff No.1 filed the PCT international application bearing No. PCT/US99/30316 on 17th December, 1999 and thereafter the national phase PCT application, bearing

No.IN/PCT/2001/00587/MUM in India on 24th May, 2001 before the Indian Patent Office claiming priority date from 23rd December, 1998. Finally the plaintiff was granted a patent IN 243917 (in short 'IN-917') generically covering millions of compounds including APIXABAN by virtue of Markush claim but it did not specifically disclose APIXABAN. IN-917 expires on 17th December, 2019. Plaintiffs are the inventors of APIXABAN and are selling the same under the brand name Eliquis®.

8. Plaintiffs in the suit plead that the defendant appears to be carrying out business of manufacturing, selling, offering for sale various generic pharmaceutical products all over India including within the jurisdiction of this Court. According to the website of the defendant i.e. www.bdrpharma.com defendant claims to be involved in the manufacture, sale and export of Active Pharmaceutical Ingredients and also engaged in its research and development. On 18th January, 2020 the plaintiffs through their credible sources received information that the defendants participated in a tender floated by Diesel Locomotive Works (DLW) regarding APIXABAN 2.5 mg. and the price for the same was quoted in the said tender. The plaintiffs' APIXABAN product 'Eliquis' has also been quoted in the said tender. Defendants did not take any authorisation or permission from the plaintiffs before dealing in plaintiffs patented APIXABAN product including supplying the generic APIXABAN product to government authorities through tender. Through the internet investigation conducted by the plaintiffs, the plaintiffs came across the website www.panjiva.com, a global supply chain intelligence provider, on which defendant No.1 has been listed as a supplier from India of 'Pharmaceutical Raw Material Apixaban' to Egypt atleast on two occasions in May, 2019 for ₹9,60,266/-. It is further

submitted that despite having the knowledge of the plaintiffs right in the suit patent, the earlier orders of this Court, protecting the plaintiffs right in suit patent, defendants have proceeded with quoting and intending to supply generic APIXABAN to government authorities. Plaintiffs also conducted a market survey in Delhi through an independent investigator and the infringing APIXABAN drug was not available in the domestic market. An affidavit on behalf of the plaintiffs was also handed over on 21st January, 2020 stating that the defendant's drug was not in the market even on that date.

9. Learned counsel for the plaintiff contends that the defendant during the course of hearing has handed-over five prior art documents and one revocation petition which has been filed seeking revocation of the suit patent i.e. IN '381' by the defendant in December 2019 only. The proposition of learned counsel for the defendant put forward that by combining the prior art documents obviousness of the suit patent can be shown is not a valid argument for the reason there should be some basis for the notional addressee being the person ordinarily skilled in the art to combine one document of prior art with the other document. The Court is also required to look into whether there is any reference in one document qua the other giving a basis to combine the two and that a combination of the two such suggestions may lead to an inventive step.

10. Learned counsel for the plaintiff relies upon the guidelines issued by the European Patent Office for examination of patent wherein it is noted that combining of two or more parts of the same disclosure would be obvious if there is a reasonable basis for the skilled person to associate these parts with one another. Though it would be generally speaking obvious to combine

two documents one of which contains a clear and unmistakable reference to the other which are considered an integral part of disclosure, however even combination of features may be an indication of the presence of an inventive step. Relying upon the decision of this Court in *F. Hoffmann-La Roche Ltd. & Anr. Vs. Cipla Ltd*. (2015) 225 DLT 391 DB it is contended that to show obviousness besides structural similarity there should be a reason or motivation shown in the prior art to make the particular structural change in order to achieve the properties that the applicant was seeking. Further, it has also to be examined whether taking the teachings in the prior document as a whole there is no teaching away from the invention. Reliance is also placed on the decision in *Eli Lilly Vs. Zenith Goldline* F.3d 1369 (Fed.Cir.2006). Referring to the decision in *Les Laboratories Servier, Adir, Oril Industries Servier Canada Inc., Servier Laboratories (Australia) Pty Ltd and Servier Laboratories Limited Vs. Apotex Inc & Apotex Pharmachem Inc*. [2008 FC 825] it is stated that a person ordinarily skilled in the art cannot simply create mosaic and there are rules of mosaicing. The party claiming obviousness should be able to demonstrate not only that the prior art exists but also as to how the person of ordinarily skilled in the art would have been led to combine the relevant components from the mosaic of prior art. Relying upon the decision of Intellectual Property Office in *Nampak Cartons Ltd. and Rapid Action Packaging Ltd*. BL 0/342/09 it is contended that though it might be tempting to put together a combination to show how the inventor may have arrived at the inventive concept, but this requires a significant degree of hindsight both in selecting the relevant disclosure from the documents and also disregarding 'irrelevant' or unhelpful teaching in them.

11. It is in the light of these arguments learned counsel for the plaintiff submits that the document of the defendant which is a publication on '*Novel Benzo-fused Lactam Scaffolds as Factor Xa Inhibitors'* by Susan Y. Tamura, et al in fact shows teachings away from APIXABAN. Further, the said publication speaks of factor Xa inhibitor based on two fused rings i.e. one lactam ring and one benzyl ring and not a lactam ring per se, which is there in APIXABAN. According to the publication, compound 5 therein is the best compound with the least IC value, thus being the most affective drug. However, compound 5 has teachings away from APIXABAN. Further, there are major differences between APIXABAN and compound 5 of the publication i.e. unlike APIXABAN methoxy is on 7^{th} carbon as a most favourable compound and there is no terminal lactam as in APIXABAN. Compound 5 has two rings one having 7 carbons and the second having 6 carbons. Further the lactam ring is at the start and not at the end as in APIXABAN which has only one lactam ring and a 6 member ring of which 5 atoms are of carbon and one atom of nitrogen. These dissimilarities and the fact that in compound 7 which has a hydrogen in it, the IC value is very high making it a very unfavourable compound there are strong teachings away from APIXABAN in this document.

12. Referring to the second document handed-over by learned counsel for the defendant to show obviousness which is a publication titled as '*Small, Noncovalent Serine Protease Inhibitors*' by Philip E.J. Sanderson learned counsel for the plaintiff stated that the said publication relates to thrombin inhibitors and not factor Xa inhibitors. The said publication notes 14 compounds which may be available to a candidate for research to start on, however none of those 14 compounds have a lactam ring much less a

terminal lactam ring. Therefore, the publication by Philip E.J. Sanderson has no teachings to be used as a starting point for a person ordinarily skilled in the art to come to APIXABAN. Rebutting the other publication by L. Leblond B., et al, in respect of '*In Vitro and in Vivo Properties of Bycyclic Lactam Inhibitors*' it is contended that this publication also deals with thrombin inhibitors and not factor Xa inhibitors. The teachings in this publication result in a compound called pyrollo-pyrazine whereas APIXABAN has pyrazolo-pyridine. Though APIXABAN has 1 nitrogen atom in the 6 member ring, compound 3 of these teachings has 2 nitrogen atoms in the 6 member ring. Further, the 5 member ring in APIXABAN in the core structure has 2 nitrogen atoms, whereas compound 3 has 1 nitrogen atom.

13. Rebutting the document of the defendant in relation to the Canadian patent of Bayer Healthcare AG, DE titled as '*Substituted Oxazolidinones and their use in the field of Blood coagulation*' it is stated that in the said claim there is no lactam ring for the reason oxygen is used in the ring. Further in none of the 254 examples cited there is a lactam ring much less a terminal lactam ring, moreover even oxazolidinone is not a terminal moiety but a core moiety.

14. Referring to the book of Kimberly A. Moore titled as '*Patent Litigation and Strategy*' learned counsel for the plaintiffs contends that most invention being combination of old elements cannot be still treated as obvious. Even in the document handed-over by learned counsel for the defendant which is a PCT application No. WO 98/16523 titled as '*Selective Factor Xa Inhibitors*' the invention relates to novel peptide mimetic analogs, their pharmaceutically accepted isomers, salts, hydrates, solvates and

prodrug derivatives and there are no teachings qua APIXABAN in this document.

15. Learned counsel for the plaintiff thus contends that the teachings in the documents noted above do not make the invention in the suit patent obvious as there are no motivations to combine the suggested references and/or most of the references teach away from the claimed invention.

16. Learned counsel for the plaintiff urges that copy of the revocation petition filed by the defendant in December, 2019 has also been handed-over, however out of the 9 exhibits relied thereon, 6 have not been supplied and out of the 3 other exhibits, one document is the claim of the plaintiff in IN '917 copy whereof is with the plaintiff and other 2 are documents '*Novel Benzo-fused Lactam Scaffolds as Factor Xa Inhibitors*' and '*Selective Factor Xa Inhibitors*'. Case of the defendant in the revocation petition is that APIXABAN is closest to Example 99 of IN '917. The plaintiffs have repeatedly stated that no product came out of or was manufactured pursuant to IN '917. There were 4 drugs which were being used as anti-coagulant in the market before APIXABAN was invented. So a person ordinarily skilled in the art would not look at the examples of IN '917 as despite 109 examples no drug was yielded and would go to the 4 existing drugs. In any case, teachings in Example 99 of IN '917 are distinct from APIXABAN, as Example 99 uses triflouro methyl (F3C) which is claimed to be changed to carboximid (H2N). Therefore, based on the documents supplied by the defendant itself, it is evident that the prior teachings were driven away from removing hydrogen as the IC value increased. Further, there are striking differences between the properties of Example 99 of IN '917 and APIXABAN inasmuch as it uses Benzene and Toluene which are

hydrophobic liquids, Phenol which is acidic and Aniline which is basic. Thus the suit patent is not obvious.

17. Relying upon the decision of this Court in *Strix Limited Vs. Maharaja Appliances Limited* MANU/DE/2174/2009 it is contended that even at the interlocutory stage, the defendant is required to place on record some acceptable scientific material supported or explained by the evidence of an expert to demonstrate that the plaintiff's patent is prima facie vulnerable to revocation. Referring to the decision of the Division Bench of this Court in *Merck Sharp and Dohme Corporation & Anr. Vs Glenmark Pharmaceuticals* 2015 SCConline Del 8227 it is contended that once the defendant launches its product it will adversely affect the plaintiff and thus an ad-interim injunction be granted in favour of the plaintiffs and against the defendants.

18. Learned counsel for the defendant contends that though the entire thrust of the learned counsel for plaintiffs in the course of the argument is that the lactam ring at the terminal end is the inventive step in the claim, however reading the complete specifications of the patent document IN '381 the focus is on the entire invention as a novelty and not merely on the lactum ring.

19. Learned counsel for the defendant contends that a comparison of the descriptions in the suit patent IN '381 and IN '917 and further IN '917 read with prior art documents leads to the conclusion that IN '381 is at the very least obvious. Further, prior art documents even excluding IN '917 also render IN '381 obvious. Written description of IN '917 which includes pharmacological data and efficacy data is identical to written description of IN '381, the suit patent. Further, written description of the U.S. counterpart

of IN '381 i.e. U.S. 208 is also identical whereas U.S. 208 is considered as a markush formula and in IN '381 APIXABAN is specifically claimed. IN '381 does not give any efficacy data over and above IN '917 claiming that the lactam ring terminally used has enhanced the efficacy. Thus, the distinction of plaintiffs' stating that IN '917 is genus and IN '381 is species is factually incorrect. Despite the data of IN '917 and IN '381 being identical there is no explanation by the plaintiff that the lactam ring was never remotely envisaged as part of IN '917. In the alternate it is also contended that since there is no difference between data specification in IN '917 and IN '381 there is no explanation about the enhancement of efficacy by the lactam ring in the suit patent, thereby leading to the inference that lactam ring was also disclosed in IN '917. The specifications in IN '381 also indicate work on thrombin inhibition de-hors the work on factor Xa inhibition.

20. To overcome the prior art, the plaintiff has sought to limit the scope of suit patent application to selective inhibition of only factor Xa which is contrary to the express language of the scope of the suit patent. From the prior art document cited by the defendants it is clear that before the priority date of suit patent, the art was moving towards a combination of lactam-based heterocyclic compounds for thrombin inhibition and factor Xa inhibition and the prior art clearly establishes that at the very least, the structure of APIXABAN without the lactam was disclosed and claimed in IN '917. Further, since the prior art had started using lactam ring in combination with heterocyclic compounds for treatment of thrombin inhibition and factor Xa inhibition, the mosaicing of the prior art documents clearly show teachings leading to combinations with lactam ring.

21. PCT application No. WO 98/16523 titled as '*Selective Factor Xa Inhibitors*' an international publication dated 23rd April, 1998 with a priority date of 11th October, 1996 specifically speaks of heterocyclic compounds which are potent and highly selective inhibitors of factor Xa and thrombin. This document also speaks of a main base moiety with a 6 member lactam ring. This document was published before the priority date of IN '917. Therefore, IN '917 read with '*Selective Factor Xa Inhibitors*' renders the suit patent obvious. In any case, there was sufficient basis for a person skilled in the art to arrive at a lactam-based heterocyclic compound through IN '917 which could have resulted in APIXABAN. Plaintiff's reply to this document that this document does not disclose a terminal lactam cannot be accepted, as the document discloses a lactam ring used with a heterocyclic compound before priority date of IN '917. Further, this invention was meant to inhibit factor Xa.

22. The publication authored by Philip E.J. Sanderson published in March 1999 titled as '*Small, Noncovalent Serine Protease Inhibitors*' recognises the use of irreversible covalent inhibitors such as beta lactams for serine protease inhibition such as thrombin and factor Xa inhibition. Thus the document which had been published before the priority date of suit patent professes the use of lactams for factor Xa and thrombin inhibition. In any case this publication renders IN '381 obvious when read in light with IN '917. Though this document focuses largely on thrombin inhibition it still remains relevant since the suit patent speaks of thrombin and factor Xa inhibition.

23. The document '*Novel Benzo-fused Lactam Scaffolds as Factor Xa Inhibitors'* published by Susan Y. Tamura, et al in 1999 also recognises that

the design of peptidomimetic inhibitors that feature lactam and related heterocyclic motifs was an active area of investigation. In fact reading IN '917 along with publication '*Novel Benzo-fused Lactam Scaffolds as Factor Xa Inhibitors'* by Susan Y. Tamura, et al, leads to the inescapable conclusion that lactam rings too were disclosed in its structure given that the structure in IN '917 clearly leads to a lactam ring. It is contended that a document to be used for obviousness need not be conclusive and only need to have teaching/ suggestion/ motivation to move in a particular direction and from the documents as noted above there was sufficient motivation for a heterocyclic compound containing a lactam ring.

24. The publication by L. Leblond B., et al, '*In Vitro and in Vivo Properties of Bycyclic Lactam Inhibitors*' in the year 2000 also notes that authors had developed potent and selective thrombin inhibitor with a novel non-peptidic structure. The rejection of this document by learned counsel for the plaintiff on the ground that it deals with thrombin inhibition is utterly dishonest as the suit patent documents also notes thrombin inhibition.

25. The document in relation to the Canadian patent of Bayer Healthcare AG, DE titled as '*Substituted Oxazolidinones and their use in the field of Blood coagulation*' with the publication date of 5th July, 2001 in Example 162 clearly shows a lactam attached to a phenyl. Example 129 of the said claim also provides the same structure and the IC value of the two structure being remarkable showing highly potent effect of lactam on factor Xa and thrombin inhibition leads to the conclusion of obviousness and lack of inventive step in IN 381. The plaintiff has deliberately not disclosed that the patent document '*Substituted Oxazolidinones and their use in the field of Blood coagulation*' has resulted in the Bayer's product Rivaroxaban and is a

competing product wherein in Example 129 terminal lactam is disclosed.

26. Any restrictive order injuncting the defendant which is not reasoned granting ad-interim injunction would be against well-settled principles of equity and contrary to the law laid down by the Supreme Court in *Ramrameshwari Devi & Ors Vs. Nirmala Devi & Ors*. (2011) 8 SCC 249

27. Since extensive arguments were addressed and number of documents were relied upon by learned counsel for the defendants despite the fact that this Court in *Strix Limited* (supra) held that even at an interlocutory stage the defendant will have to place on record some acceptable scientific material, supported and explained by evidence of an expert that the plaintiff's patent is prima facie vulnerable to revocation and no such expert evidence has been placed on record much less on an affidavit, this Court is proceeding to examine the contentions urged by learned counsel for the defendants to ascertain whether defendants have made out a case for revocation of the suit patent and in the light thereof whether the triple test laid down for grant of injunction i.e. a prima facie case, irreparable loss and balance of convenience is satisfied or not.

28. Before proceeding further this Court would like to note the difference between the Thrombin Inhibitors and Factor Xa Inhibitors in blood coagulation. Blood coagulation cascade involves a complex series of activation reactions which ultimately lead to generation of thrombin which converts fibrinogen to fibrin resulting in coagulation of the blood. Claim of the plaintiffs is that most of the earlier studies have worked on thrombin inhibition so as to act as an anti coagulant whereas the plaintiff's invention is Factor Xa inhibitor which inhibits the production of thrombin itself. The distinction between Thrombin inhibitors and Factor Xa inhibitors and the

advantage of Factor Xa inhibitors besides the advantages new compound should have been highlighted in the claim specifications of the suit patent IN-381 as under:-

> *"Activated factor Xa, whose major practical role is the generation of thrombin by the limited proteolysis of prothrombin, holds a central position that links the intrinsic and extrinsic activation mechanisms in the final common pathway of blood coagulation. The generation of thrombin, the final serine protease in the pathway to generate a fibrin clot, from its precursor is amplified by formation of prothrombinase complex (factor Xa, factor V, Ca^{2+} and phospholipid). Since it is calculated that one molecule of factor Xa can generate 138 molecules of thrombin (Elodi, S., Varadi, K.:Optimization of conditions for the catalytic effect of the factor IXa-factor VIII Complex: Probable role of the complex in the amplification of blood coagulation. Thromb. Res. 1979. 15. 617-629) inhibition of factor Xa may be more efficient than inactivation of thrombin in interrupting the blood coagulation system.*
>
> *Therefore, efficacious and specific inhibitors of factor Xa are needed as potentially valuable therapeutic agents for the treatment of thromboembolic disorders. It is thus desirable to discover new factor Xa inhibitors. In addition, it is also desirable to find new compounds with improved pharmacological characteristics compared with known factor Xa inhibitors. For example, it is preferred to find new compounds with improved factor Xa inhibitory activity and selectivity for factor Xa versus other serine proteases (i.e., trypsin). It is also desirable and preferable to find compounds with advantageous and improved characteristics in one or more of the following categories, but are not limited to: (a) pharmaceutical properties (e.g., solubility, permeability, and amenability to sustained release formulations); (b) dosage requirements (e.g., lower dosages and/or once-daily dosing); (c) factors which decrease blood concentration peak-to-trough characteristics (e.g., clearance and/or volume of distribution); (d) factors that increase the concentration of active drug at the receptor (e.g., protein binding, volume of distribution); (e)*

factors that decrease the liability for clinical drug-drug interactions (e.g., cytochrome P450 enzyme inhibition or induction); (f) factors that decrease the potential for adverse side effects (e.g., pharmacological selectivity beyond serine proteases, potential chemical or metabolic reactivity, and limited CNS penetration); and, (g) factors that improve manufacturing costs or feasibility (e.g., difficulty of synthesis, number of chiral centers, chemical stability, and ease of handling)".

29. Learned counsel for the defendants have not disputed that the defendants have applied for tenders for sale of APIXABAN and the challenge to the suit patent in the course of arguments is based not on anticipation but on obviousness. Section 64(1)(f) of the Patents Act provides as under:

> "64. (1) Subject to the provisions contained in this Act, a patent, whether granted before or after the commencement of this Act, may, [be revoked on a petition of any person interested or of the Central Government by the Appellate Board or on a counter-claim in a suit for infringement of the patent by the High Court] on any of the following grounds that is to say-
>
> > (f) that the invention so far as claimed in any claim of the complete specification is obvious or does not involve any inventive step, having regard to what was publicly known or publicly used in India or what was published in India or elsewhere before the priority date of the claim: [***]"

30. Before analyzing the documents relied upon by learned counsel for the defendants to show that by mosaicing and dehors mosaicing from the documents of prior art it is evident that the suit patent is obvious and there are teachings to move in the direction of a lactam ring which is the main plank of the plaintiffs' arguments to show inventive step, it would be appropriate to note the principles laid down in various decisions to test

whether the prior art makes the invention obvious.

31. In *F. Hoffmann-La Roche Ltd. & Anr. Vs. Cipla Ltd* (*supra*) the Division Bench of this Court noted the concept of teaching away and hindsight argument to test the defence of obviousness and held:

> "117. *Expressing a note of caution, the Bombay High Court in F.H. & B. Corp. (supra) guarded the Courts of law against the common human failing of being wise after the event in regarding something that has been discovered by research as obvious. In Grain Processing (supra) the Court noted that care must be taken to avoid hindsight reconstruction by using the patent in suit as a guide through the MAZE of prior art references in the right way so as to achieve the result of the claims in suit. In Pfizer Inc. Vs. Teva Pharmaceuticals (supra) it was held that a patent challenger however must demonstrate the selection of a lead compound based on its promising useful properties, not a hindsight driven search for structurally similar compounds. Similar caution was advanced in Yamanouchi Pharmaceutical Co. Ltd. (supra) and Otsuka Pharmaceutical Co. Ltd.(supra).*
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> 119. *On the various tests as noted above, there is no dispute between Cipla and Roche however the dispute arises whether the teaching of prior art document should be considered as a whole, whether there should be no teachings away and whether evidence to try merely on structural similarity can form the basis for selection of lead compound in a prior art.*
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> 121. *In re: Dillon relied upon by learned counsel for Cipla, though the majority held that a prima facie case for obviousness of chemical composition is established if there is structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, and if prior art gives reason or motivation to make claimed composition however, the minority judgment noting various authorities held that Courts have expressed dissatisfaction on the earlier rule that 'structural obviousness' alone was deemed to create a presumption of unpatentability. The minority held that the*

weight of the authorities would show that structural similarity of the prior art compound cannot be the criteria alone and the prior art must prima facie suggest both similar structure and property before the burden shifts to the applicant to prove the unexpected differences. Even in 444.2d 581 re: John R. Slemniski the Court held that similarity of structure alone was insufficient for prima facie unpatentability. Thus to show obviousness besides structural similarity there should be a reason or motivation shown in the prior art to make the particular structural change in order to achieve the properties that the applicant was seeking."

32. In *Eli Lilly Vs. Zenith Goldline* (*supra*) it was held:

"While Chakrabarti 1980a suggests that a chlorine atom in place of the fluorine atom would also enhance the compound's activity, it does not specifically suggest that the same result could be obtained with a hydrogen atom. Nichols Tr. 2779: 17-24; TX 3465 at 879, col. 2. Nor does anything in Sullivan and Franklin suggest the desirability of using a hydrogen atom at this position. Nichols 2776:5-11; TX 3161; Findings of Fact § IV. B.I.d. If one were looking to replace the fluorine, one would replace the fluorine with other electronegative groups, not hydrogen. TX 1315 at 3172; LaVoie Tr. 1572:12-1573:18. Indeed, the art as a whole teaches directly away from using hydrogen because it is not an electron-withdrawing substituent.

Likewise, in this case, the defendants have not shown that a person ordinarily skilled in this art would have selected Compound `222 as a lead compound because it contained hydrogen rather than fluorine or chlorine. At the time of invention, the state of the art would have directed the person of ordinary skill in the art away from unfluorinated compounds like Compound `222. After all, the primary example of the state of the art at that time, the `574 patent, did not provide any biological data for compound `222, suggested a preference for halogen-containing compounds, and identified a fluorine-containing compound, ethyl flumezapine, as "particularly active." Findings of Fact and Conclusions of Law, 364

F.Supp.2d at 904. Moreover, as the trial court detailed, Chakrabarti 1980a expressly taught that the addition of a fluorine or chlorine enhanced anti-psychotic activity. It also taught that the unfluorinated Compound `222 was less active than the benchmark compound, clozapine. Id. Thus, rather than providing the requisite motivation, the prior art taught away from selecting Compound `222 as a lead compound for further development."

33. In respect of mosacing prior art document in the decision *Les Laboratories Servier, Adir, Oril Industries Servier Canada Inc., Servier Laboratories (Australia) Pty Ltd and Servier Laboratories Limited Vs. Apotex Inc & Apotex Pharmachem Inc*. (*supra*) it was held:

"254. As acknowledged by Servier, a mosaic of prior art may be assembled in order to render a claim obvious. Even uninventive skilled technicians would be presumed to read a number of professional journals, attend different conferences and apply the learnings from one source to another setting or even combine the sources. However, in doing so, the party claiming obviousness must be able to demonstrate not only that the prior art exists but how the person of ordinary skill in the art would have been led to combine the relevant components from the mosaic of prior art. This case is a good example. Apotex asks the Court to conclude that a person of ordinary skill in the art, without inventiveness or ingenuity, could collate a relatively large number of discrete pieces of knowledge from a lengthy list of prior art on ACE inhibitors (and even some sources outside the ACE inhibition field), make some fundamental assumptions and combine this knowledge to come up with a perindopril molecule.

255. Another factor that makes the task more difficult is that, as conceded by Dr. Marshall, small changes in structure can have unpredictable pharmacological effects.

256. The experts produced by Apotex who spoke to this issue focussed on each of the individual component from the prior art. When speaking of the obviousness of the 6, 5 bicyclic ring,

none of those experts effectively explained how a person skilled in the art would have known to combine all of the disclosures of the prior art to come up with perhydroindole ring structure. I accept that there were suggestions in the prior art that such a ring might work. However, combining all of the suggestions of the prior art is, in my view, likely a task that required ingenuity and inventiveness. Overall, I prefer the expert evidence of Drs. Trost, Bartlett and Cimarusti."

34. In *Nampak Cartons Ltd. and Rapid Action Packaging Ltd* (*supra*) it was held:

"46. It might be tempting to put together a combination of eg. Spiral Packs, Rigby and Meyers to show how the inventor may have arrived at the inventive concept; but this requires a significant degree of hindsight, both in selecting the relevant disclosures from these documents and also in disregarding the 'irrelevant' or unhelpful teaching in them. As the fourth Windsurfing step makes clear, the assessment must be made "without any knowledge of the alleged invention as claimed". Furthermore, there are no cross-references between any of these documents, and there is no suggestion that any of them would have been well known. There is also no evidence that any of the relevant packages in Spiral Packs, Rigby or Meyers had been put into use by 2002 — if anything, the evidence indicates that they had not. All these factors argue against combining prior art documents such as Spiral Packs, Rigby and Meyers.

47. I have found that the difference between each of the prior art documents relied upon in these proceedings and the inventive concept in the patent constitutes one or more steps that would not have been obvious to the person skilled in the art. The application to revoke the patent is therefore unsuccessful."

35. In *Technograph Printed Circuits Limited v. Mills & Rockley (Electronics) Ltd.* [1972] R.P.C. 346 dealing with the scope of an invention being obvious, it was held:

"To whom must the invention be obvious? It is not disputed that the hypothetical addressee is a skilled technician who is well acquainted with workshop technique and who has carefully read the relevant literature. He is supposed to have an unlimited capacity to assimilate the contents of, it may be, scores of specifications but to be incapable of a scintilla of invention. When dealing with obviousness, unlike novelty, it is permissible to make a "mosaic" out of the relevant documents, but it must be a mosaic which can be put together by an unimaginative man with no inventive capacity.

XXX XXX XXX

Whether or not it was obvious to take a particular step is a question of fact; it was formerly left to a jury. But the question is not whether it is now obvious to the court (or to the jury) but whether at the relevant date it would have been obvious to the unimaginative skilled technician. A thing which now seems obvious to anyone may at that date have been far from obvious to him. In this case he would have been faced with a large variety of different methods, none of which had proved commercially useful. He would have had no assurance that any successful solution was possible, still less would he have known in what direction to look for it. He would be expected to try out all obvious modifications or combinations of these methods which seemed to him worth trying.

Some importance was attached by the appellants to a question formulated by Sir Stafford Cripps and cited in Sharp and Dohme Inc. v. Boots Pure Drug Co. Ltd. (1928) 45 R.P.C. 153 at p. 173.

> *"The real question is: was it for all practical purposes obvious to any skilled chemist in the state of chemical knowledge existing at the date of the patent...that he could manufacture valuable therapeutic agents by making the higher alkyl resorcinols."*

I do not think that this means that the hypothetical technician must try every possible permutation or combination of existing methods. That might be an endless task. In the passage which I have just cited there is the word "valuable". So what he must be supposed

to have done is to try everything which would appear to him as giving any prospect of valuable results."

36. From the judgments as noted above, some of the principles which govern the field to find out whether an invention is obvious or not can be summed up as under:-

(i) A hindsight reconstruction by using the patent in question as a guide through the maze of prior art references in the right way so as to achieve the result of the claim in the suit, is required to be avoided.

(ii) The patent challenger must demonstrate the selection of a lead compound based on its promising useful properties and not a hindsight driven search for structurally similar compounds.

(iii) There should be no teachings away from the patent in question in the prior art.

(iv) Mere structural similarity cannot form the basis of selection of lead compound in a prior art and the structural similarity in the prior art document must give reason or motivation to make the claim composition.

(v) Though mosaic of prior art documents may be done in order to claim obviousness, however, in doing so, the party claiming obviousness must be able to demonstrate not only the prior art exists but how the person of ordinary skill in the art would have been led to combine the relevant components from the mosaic of prior art.

(vi) It has to be borne in mind, small changes in structures can have unpredictable pharmacological effects and thus, structural similarity alone is not sufficient to motivate to selection of the lead compound.

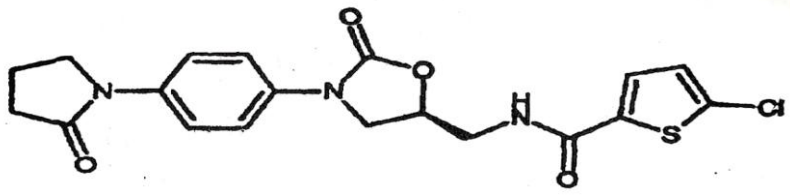
(vii) Though it would be tempting to put together a combination of prior arts but this requires a significant degree of hindsight, both in selection of relevant disclosures from these documents and also in disregarding the irrelevant or unhelpful teachings in them.

37. The Court of Appeals in '*The General Tire & Rubber Company V. The Firestone Tyre & Rubber Company Limited & Ors*.' 1972 R.P.C. held that to find out what is obvious one does not have to look upon beyond the primary dictionary meaning of it which says 'very plain'. Thus, the requirement for an invention to be obvious under Section 64(1)(f) should involve that the complete specification should be obvious, or it does not involve any inventive step, having regard to what was publically known or publically used in India or what was published in India or elsewhere before the priority date of the claim. Even accepting the fact that for a person ordinarily skilled in the art of average intelligence, publications prior to the prior art were known to him, in most of the documents there are teachings away from lactam ring much less a terminal lactam and even by mosaicing the relevant documents by an unimaginative man with no inventive capacity they do not lead to the suit patent being obvious.

38. As noted above, it is thus well settled that in case prior art document show a concept of teaching away from the inventive step, the said prior art document cannot be used to demonstrate that the invention is obvious and thus not liable to be patented. The publication by Susan Y Tamura, et al as noted above is bicyclic having a lactam ring and a fused benzyl ring and there is no lactam ring per se much less a terminal lactam ring. Table 1 in the publication notes compound 5 as the most favourable compound and compound 7 as the most unfavourable compound with high IC Value and hydrogen therein. Thus, this publication would give motivation to work on compound 5 with least IC value, hence most favourable, however the said compound clearly has teachings away from APIXABAN which has hydrogen therein. This publication also cannot be treated as a prior art for a

person ordinarily skilled in the art for the reason besides the lactam ring composition of the rings is also different as it teaches 6 carbon atoms together which give the worst biological activity. The publication itself notes that in all these new compounds, compound 5 expressed favourable in vitro potencies against uncomplex factor Xa and that further investigation of their application will be reported in due course. Even the publications by Philip E. Sanderson and L. Leblond, et al, do not show prior teachings for the reason the same are not based on factor Xa inhibitors but on thrombin inhibitors. None of the compounds stated in the publication by Philip E.J. Sanderson use a lactam ring much less a terminal lactam.

39. The main plank of the argument of learned counsel for the defendant to show obviousness of the suit patent is the Canadian patent of Bayer Healthcare AG, DE titled as '*Substituted Oxazolidinones and their use in the field of Blood coagulation*' and their use in the field of blood coagulation which document demonstrates a compound with a lactam ring with phenyl therein. From Example 17 of the said claim of the Canadian patent CA 2396561 drug Rivaroxaban was manufactured and used as an anti-coagulant before the priority date of IN '381. The structural formula of Example 17 is as under which consists of 5-Chloro-N-({(5S)-2-oxo-3-[4-(2-oxo-1-pyrrolldinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide called Thyphene carboxymide methyl oxyzolidinone.



However, in the said claim the IC value of Example 127 is better than Examples 129 and 162 and far superior than Example 17. Hence, this compound made from Example 17 of CA 2396561 does not give a motivation for making a compound with the lactam ring and the best Example being 127 which has the least IC value being 0.0007 does not have a lactam ring on the left side but a morphalenone moiety. The claim in this patent of Bayer Healthcare AG, DE uses an oxygen atom in the ring which is thus not a lactam ring. Further, none of the 254 examples in the said claim has a lactam ring much less a terminal lactam ring and even oxazolidin -2-1 is not a terminal moiety but a core moiety.

40. In the PCT application No. WO 98/16523 relied upon by learned counsel for the defendant, the invention relates to selective factor Xa inhibitors from peptide and peptide mimetic analogs, their isomers, salts, hydrates, solvates, etc. and has no teachings qua APIXABAN. This application by COR THERAPEUTICS. INC. US was for factor Xa inhibitors, wherein the lactam ring is a central lactam ring and not a terminal lactam ring and with a double bond oxygen. A perusal of the examples of CA 2396561 shows that oxazolidinone is common to all the compounds.

41. The defendant's argument is also based on the revocation petition filed in December, 2019 wherein it is claimed that Example 99 of IN '917 is close to APIXABAN. However, as noted above, prior art documents show teachings away from removal of hydrogen. Besides there are fundamental differences in Example 99 and APIXABAN.

42. Contention of learned counsel for the defendants that the suit patent specifications also notes thrombin inhibitors ignores the fact that the claim of the plaintiffs in IN '381 is based on factor Xa inhibitor even though in the

document thrombin inhibitors may be noted.

43. Learned counsel for the defendant has strenuously argued that comparison of the descriptions in the suit patent IN-381 and IN-917 shows that the two are similar, leading to the conclusion that IN-381 is at the very least obvious and even excluding IN-917 pharmacological data and efficacy data being identical with IN-917 and US 208, the suit patent IN-381 does not demonstrate an enhanced efficacy as required under Section 3(d) of the Patents Act.

44. Section 3(d) of the Patents Act reads as under:

> *"3. What are not inventions.—The following are not inventions within the meaning of this Act,—*
>
> XXX XXX XXX
>
> XXX XXX XXX
>
> *(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*
>
> *Explanation.—For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy".*

45. This Court has already noted that no drug came out of IN-917 and the first marketable drug came pursuant to the suit patent IN-381 which itself is sufficient to show enhanced efficacy.

46. In *Ramrameshwari Devi & Ors (supra)* relied upon by the learned

counsel for the defendants, Supreme Court held that ex parte ad interim injunction should be granted only in exceptional cases and ordinarily, Courts should issue short notices to the defendants and pass appropriate orders only after hearing the parties concerned. In the present case, the defendants have been heard extensively before granting ad interim injunction. Further in *Ramrameshwari Devi & Ors (supra)*, the Supreme Court was dealing with a case where the appellant before it had seriously created obstacles at every stage during the course of trial and virtually prevented the Court from proceeding with the suit. It is in the light of these facts, the Supreme Court laid down steps for Trial Courts for improving the existing system and that realistic costs should be determined and imposed by the Courts in cases of frivolous litigations causing harassment to the opposite party and wastage of Court's time. The decision of the Supreme Court thus does not apply to the facts of this case as no material has been shown at the moment to show that false, fabricated or manipulated proceeding are instituted by the plaintiffs against the defendants.

47. Consequently, the defendant admitting tendering and intending to sell the plaintiff's drugs APIXABAN thereby amounting to infringing the plaintiff's suit patent, the plaintiff has made out a prima facie case, as the suit patent on the basis of the prior art documents relied upon is not amenable to revocation for being obvious. In case no interim injunction is granted, the plaintiffs would suffer an irreparable loss as held by the Division Bench of this Court *Merck Sharp and Dohme corporation & Anr*. 2015 SCConline Del 8227. The balance of convenience also lies in favour of the plaintiffs and against the defendants as the defendants have not commercially sold APIXABAN in the open market as yet but has only filed

tenders for the same. Consequently, an ad-interim injunction is granted in favour of the plaintiffs and against the defendants in terms of prayer 'A' of Para 17 of the application.

48. Reply affidavit to the application be filed within three weeks. Rejoinder affidavit in two weeks thereafter.

49. List the application before Court on 31st March, 2020.

(MUKTA GUPTA)
JUDGE

JANUARY 30, 2020
'ga'

HIGH COURT OF DELHI
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