IN THE HIGH COURT AT CALCUTTA
(Intellectual Property Rights Division)
ORIGINAL SIDE

BEFORE:
The Hon'ble Justice Ravi Krishan Kapur

IPDPTA/119/2023
IN THE MATTER OF:

TAKEDA PHARMACEUTICAL CO LTD
VS
CONTROLLER OF PATENTS AND DESIGNS AND ORS.

For the appellant : Ms. Swati Mittal, Advocate
Mr. Abhirup Chakraorty, Advocate
Mr. Varun Sharma, Advocate
Ms. Manisha Singh, Advocate
Ms. S. Singh, Advocate

For the respondent nos. 1 and 2 : Mr. N. L. Singhania, Advocate
Mr. Sunil Kumar Singhania, Advocate

Judgment on : 11 April 2025

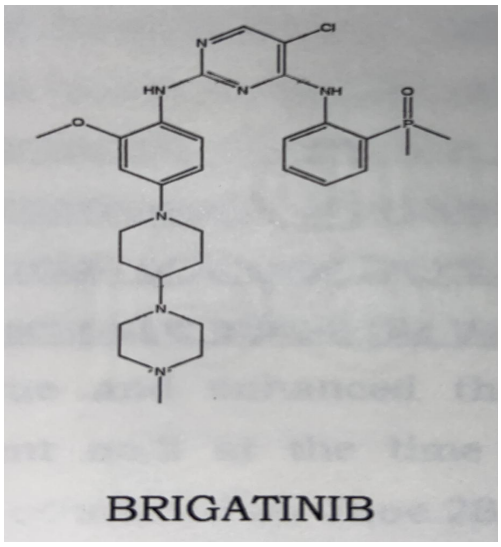
RAVI KRISHAN KAPUR, J.:

1. This is an appeal against an order dated 12 April 2023 passed by the Deputy Controller of Patents & Designs (the respondent no. 2), rejecting an application for patent being Patent Application No.3939/KOLMP/2010 on the grounds of lack of inventive steps under section 2 (1) (ja), 3(d) and section 10(4) of the Patents Act 1970.

2. The application was filed with the Patent Office, Kolkata on 21 October 2010 claiming priority from PCT application PCT/US/2009/044918 filed on 21 May 2009. The invention relates to Novel Protein Kinase Inhibitors. Protein Kinase which represents a large family of proteins plays a crucial role in the regulation of a wide variety of cellular process and maintains control over

cellular function. One of the main objects of the invention is to provide a new class of compounds with increased Inhibitory “selectivity” towards a specific protein Kinase which is useful in the treatment of protein kinase related diseases such as cancer.

3. The application provides a new class of potent and selective ALK inhibitors. It is contended that the compounds of the subject invention, including the claimed compound, are inhibitors of ALK. The subject application relates to a single compound, Brigatinib, comprising a pyrimidine core being connected to a phenylpiperidinylpiperazinyl three ring moiety at 2- position via a NH linker and said pyrimidine core also being connected to a phenyl ring substituted with a dimethyl phosphoryl group at 4- position via another NH linker. Thereafter, the said pyrimidine core is substituted with a chloro at 5- position and is non substituted at 6- position. The claimed compound has the following structure:



4. The said invention claims to have several important Kinase targets and exhibit preferences for inhibiting some kinases over others as well as variations in pharmacokinetic profiles and confirms that this class of

compounds (phosphorous derivatives) is of significant interest as a source of potential pharmaceutical agents. Brigatinib falls within the same class of compounds and it is highly selective for inhibition of one such protein kinase named ALK over others similar protein kinase such as Ins-R.

5. Ins R is an insulin receptor and impaired Ins-R activity could lead to insulin resistance, the key factor in the pathology of metabolic disorders including type 2 diabetes mellitus. Thus, it becomes important that kinase inhibitor compounds should be very selective such that while inhibiting ALK, for treatment of cancer, those should not inhibit Ins-R. The subject application clearly provides that the technical objective is to provide such selectivity.

6. At the time of filing the application, the appellant had claimed a group of compounds represented by a Markush structure covering the compound Brigatinib. However, during prosecution of the subject application, the appellant opted to select and proceed with a single specific compound called 'Brigatinib'. Brigatinib is identified to exhibit increased selectivity for ALK, over Ins-R due to substantially decreased binding affinity towards Ins-R as reflected by increased IC50 value, which results in superior therapeutic efficacy due to reduced competitive binding to Ins-R, which consequently decreased deleterious side effects which are caused by disruption of normal functions due to non-targeted binding to Ins-R, which seriously affects a patient's health. The data for increased IC50 value and enhanced therapeutic efficacy had also been furnished at the time of filing of the post hearing submissions.

7. The said application was examined under section 12 and 13 of the Act and the First Examination Report (FER) was issued on 15 February 2016. The

appellant submitted its response to the said FER on 22 August 2016 with the amended claims and other corresponding documents. Thereafter, the appellant received a hearing notice dated 31 March 2017. After several adjournments the matter was finally heard on 28 June 2017.

8. During the hearing, the respondent no.2 maintained the objections raised under section 2 (1) (ja) of the Act i.e. lack of inventive steps and section 3(d) of the Act i.e. patentability in view of the following cited prior art documents:

a. D1: US2005/203114
b. D2: US6878697
c. D3: WO 2006/078846
d. D4: WO 2005/016528
e. D5: WO 2007/006926
f. D6: WO 2007/021937
g. D7: WO 2004/080980

9. Subsequently, the appellant filed its Written Submissions alongwith the amended claim and an affidavit to establish the advantageous characteristics of the claimed compounds. The appellant also filed an additional Written Submission to comply with the formal requirements and to further restrict the scope of the claim to a single compound and narrow down the original claims relating to the Markush structure covering group of compounds to a single compound amongst the entire plurality of compounds covered by the Markush structure.

10. Subsequent to filing of the said written submissions, two pre-grant oppositions were filed against the appellant one by the “Cancer Patients Aid Association” and the other by Ms. Mita Sheikh on July 2017 and 11 September 2018 respectively. Both these pre-grant oppositions raised similar objections of lack of novelty and prior publication under section 25(1)(b), prior

public knowledge or public use in India under section 25(1)(d), obviousness and lack of inventive steps under section 25(1)(e) of the Act.

11. It is contended that the respondent no 2 ignored the submissions and the evidence relied on by the appellant. The impugned order has been passed without any application of mind and is based on mere assumptions and an incorrect understanding of the invention as well as the prior arts. It is further alleged that the impugned order has been passed in violation of the principles of natural justice and is devoid of reason. The respondent erred in not considering the supplementary experimental data and subsequent affidavits which would demonstrate the improved selectivity of Brigatinib for ALK over Ins-R, technical advancement and enhanced therapeutic efficacy possessed by Brigatinib over the closest compounds known in the art. The supplementary data does not present any new or additional features of the claimed invention as has been held by the respondent no. 2. It is alleged that the opponents and the respondent no. 2 have in hindsight searched for similar looking structures and have then replace the "Sulfonyl Group" without assigning any reason as to why the said particular group ought to be replaced from TAE-684. There has also been a failure of the respondent no.2 in not appreciating that a difference of even one functional group can drastically alter the properties of a compound.

12. On behalf of the respondent it is contended that the claims made by the appellant in the subject invention were not allowable under section 25 (1)(e), 25 (1)(f) and 25 (1)(g) of the Act. The impugned order is well-reasoned and does not warrant any interference. It is contended that the claimed invention differs in the presence of 'phosphoryl group' to get compound 'Brigatinib'

instead of 'sulfonyl group' of the prior arts. The technical advancement in the present case may be regarded as 'increase in the selectivity' of 'Brigatinib' for ALK over InS-R. The appellant also failed to furnish any evidence of technical advancement nor of effectiveness of the compound 'Brigatinib' at the time of filing the complete specification.

13. The impugned order has found that the claims of the appellant are obvious in view of the fact that the replacement of 'sulfonyl group' by 'phosphoryl group' is obvious to a person skilled in the art making the claim lack any inventive steps. Secondly, the appellant failed to furnish any documents to demonstrate any technical advancement of the subject invention. Thirdly, assuming that the appellant was unaware of the technical advancements at the time of filing of the specifications, the invention lacked sufficient disclosure.

14. In *Avery Dennison Corporation* v. *Controller of Patents and Designs* (2022/DHC/004697), it has been held as follows:

Test for Inventive Step/Lack of Obviousness

10. In order to decide this issue, some of the fundamental principles for determining the existence of an inventive step and the lack of obviousness need to be emphasised.

11. For determining inventive step or lack thereof, various approaches and tests have emerged over the years from decisions of courts/authorities as also from examination guidelines of patent offices from different jurisdictions. The same include:

i. Obvious to try approach:

• *This approach involves an analysis of whether in view of the teachings/solutions proposed in the prior art, it was obvious to try and arrive at the subject invention.*

ii. Problem/solution approach:

• *This approach considers whether in the light of the closest prior art and the objective technical problem, the solution claimed in the invention would be obvious to the skilled person. If the skilled person can decipher the solution being claimed, then the subject matter is held to be obvious.*

• *This test has been discussed by the Division Bench in* F. Hoffmann-La Roche Ltd. *v.* Cipla Ltd., *(2016) 65 PTC 1 (Del).*

iii. Could-Would Approach

• *In this approach the question that is raised is whether there is any teaching in the prior art as a whole that would and not simply could have prompted a skilled person, with the knowledge of the objective technical problem, to either modify or adapt the closest prior art to arrive at the subject matter of the claims.*

iv. Teaching Suggestion Motivation (TSM test)

• *This test originated in the USA as per which, if by the Teaching, Suggestion or Motivation from the prior art, an ordinary skilled person can modify the prior art reference or combine prior art references to arrive at the claimed invention, then the subject matter being claimed is obvious.*

• *However, the application of this test ought not to be done in a narrow manner as held by the US Supreme Court in the case of* KSR International *v.* Teleflex, *550 US 398 (2007).*

15. In determining inventive steps, the invention should be considered as a whole. In other words, it is not sufficient to draw the conclusion that a claimed invention is obvious merely because individual parts of the claim taken separately are known or might be found to be obvious or structurally similar to that of the compound claimed. The contention that an invention is obvious in relation to a particular item must be treated with care and caution. In doing so, the whole picture presented should be taken into consideration and not a selective one. There should be an element of preciseness about what is asserted to be common general knowledge. The "obviousness" must also be strictly and objectively judged. [*Bishwanath Prasad Radhey Shyam v. Hindustan Metal Industries, (1979) 2 SCC 511 paras 24 & 25, F.*

Hoffman La Roche Ltd. v. Cipla Ltd. 2015 SCC OnLine Del 13619 and *Groz-Beckert KG v. Union of India (2023 SCC OnLine Cal 111*)].

16. In passing the impugned order, the respondent no.2 has found that Brigatinib differs from TAE684 only due to presence of 'phosphoryl group' instead of 'sulfonyl group' of prior arts and that the replacement of 'sulfonyl group' by 'phosphoryl group' in the claimed compound. Brigatinib is obvious on the basis of Zhao et. al 1999, Zhao et. al 1998_5, Zhao et. al 1998_8 (collectively referred to as "Zhao") and Schneider et al which disclose Bioisosterism between the two groups. The experimental data and evidence relied on by the appellant has been totally ignored in passing the impugned order. Moreover, the respondent no.2 failed to apply the settled principles for assessment of inventive steps and erred in appreciating the true scope of the invention. The contention raised on behalf of the appellant that there is no clue nor motivation to modify the structure of TAE684 disclosed in WO'980 to arrive at Brigatinib even upon considering the bioisosterism teachings of the prior art has not been adverted to. Further, as contended Zhao does not teach discovery of bioisosterism with regard to herbicidal activity among herbicidal compounds which would extend to therapeutics, let alone therapeutics that show selective activity has not even been considered in the impugned order. Thus, a person skilled in the art would not even consider the Zhao references as relevant to the possible modification of TAE684.

17. In *F. Hoffmann-La Roche Ltd.* v. *Cipla Ltd.*, 2015 SCC OnLine Del 13619, it has been held as follows:

> *"152. 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. *v.* 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).*

153. From the decisions noted above to determine obviousness/lack of inventive steps the following inquires are required to be conducted:

Step No. 1 To identify an ordinary person skilled in the art,

Step No. 2 To identify the inventive concept embodied in the patent,

Step No. 3 To impute to a normal skilled but unimaginative ordinary person skilled in the art what was common general knowledge in the art at the priority date.

Step No. 4 To identify the differences, if any, between the matter cited and the alleged invention and ascertain whether the differences are ordinary application of law or involve various different steps requiring multiple, theoretical and practical applications,

Step No. 5 To decide whether those differences, viewed in the knowledge of alleged invention, constituted steps which would have been obvious to the ordinary person skilled in the art and rule out a hideside approach."

18. In *Bristol-Myers Squibb Holdings Ireland Unlimited Company* v. *BDR Pharmaceuticals International Pvt. Ltd.*, 2020 SCC OnLine Del 1700, it has also been held as follows:

"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."

19. In view of the above, the respondent no.2 erred in not considering the submissions of the appellant and the evidence on record to refute the claims of respondent nos.3 & 4 as mentioned in the replies filed to the pre-grant opposition. Mere structural similarity between compounds of the prior arts and the claimed invention does not make the entire invention obvious. The respondent no.2 also failed to furnish any reasons in concluding that the compounds were structurally similar and how the teachings of the invention were obvious.

20. In respect of the issues raised in view of the technical advancement, the appellant had filed specifications which disclosed the effectiveness of few exemplified compounds which demonstrate the IC50 value less than 1nM.

Diverse evidence was brought on record by the appellant to demonstrate that Brigatinib is identified to exhibit increased selectivity for ALK, over Ins-R due to substantially decreased binding affinity towards Ins-R as reflected by increased IC50 value, which consequently resulted in superior therapeutic efficacy resulting in reduced competitive binding to Ins-R, and consequently decreased deleterious side effects that are caused by disruption of normal functions due to non-targeted binding to Ins-R, which seriously affects the patient's health. All such technical and scientific evidence has been ignored and has not even been considered in the impugned order.

21. The respondent no 2 also failed to consider the oral and written submissions filed during the hearing and subsequently erred in restraining the appellant from filing any further submissions in respect of the subject claim. The subject invention is a pharmaceutical compound. It is well established that development of pharmaceutical drug is a lengthy process and the data to demonstrate therapeutic efficacy can be filed even after filing of specification. No time bar has been provided in the Act which prevents an applicant from filing additional documents after filing of the patent claim. Any evidence which shows technical advancement deserved to have been considered in deciding the existence of technical effect. *[Oyster Point Pharma Inc vs Controller of Patents and Designs & Anr, 2023 SCC Online Cal 1214* and *Astrazeneca vs Intas Pharmaceuticals Ltd, 2020 SCC Online Del 2765].*

22. In the impugned order, the respondent no.2 has made contradictory findings in concluding that even though the appellant has disclosed a process for preparation of "Brigatinib" since the subject matter relates to a compound by displaying a process (only) for preparation of the said drug the same did not

fulfil the requirements of section 10(4) of the Act and that the appellant was not aware if "Brigatinib" exhibits any ALK inhibitory activity. Brigatinib was selected while narrowing down the claims at the time of prosecution of the subject invention from the class of compounds claimed as Markush structure. Further, in a claim relating to a novel compound, the requirement of sufficiency of disclosure is satisfied, if the structure of compound and the method for the preparation of said compound is disclosed, as it enables a person skilled in the art to perform the invention. Initially, the respondent no.2 did not find such insufficiency in the FER. It was only when raised by the opponent did the respondent no.2 in hindsight refuse the subject application on these grounds. Significantly, the European Patent Office had granted the same compound without raising any objection on insufficiency and the entire evidence in this regard has been ignored in passing the impugned order.

23. The respondent no. 2, despite quoting various parts of subject application in the impugned order, has failed to comprehend the invention in its correct perspective. The respondent no.2 also failed to apply the correct approach required to evaluate the matter for requirement of sufficiency of disclosure under section 10(4) of the Act which ought to have been applied. The respondent No. 2 has applied section 10(4) on the basis of lack of data related to establish unexpected technical effects for inventive step and therapeutic efficacy as required to neutralize non-patentability under section 3(d) of the Act. The requirement under section 10(4) of the Act relates to fully and particularly describing the invention and its operation or use and the method

by which it is to be performed. Section 10(4) of the Act does not require to demonstrate any kind of data or efficacy which is not part of the claim.

24. The respondent no.2 had also ignored nor dealt with the data which would demonstrate the technical advancement and significant industrial acclaims attained by Brigatinib namely a) US FDA approval for Brigatinib as front-line therapy for ALK-positive metastatic non-small cell lung cancer, due to superior longer progression-free survival (PFS) of the patients who received Brigatinib as compared to other drugs available in the art, b) articles published in peer-reviewed journals of high impact factor, which demonstrates advantageous effects of Brigatinib through comparative analysis of Brigatinib and the other drugs available in the art, and c) expert evidence by way of affidavit. This has not ever been considered in the impugned order.

25. Additionally, in passing the impugned order the respondent no.2 has failed to give any weightage to the fact that the requirement of inventive steps and the tests applied to assess the same are more or less universal across different patent jurisdictions, and the fact that the invention had been registered in more than 50 countries.

26. In *F. Hoffmann-La Roche Ltd. v. Cipla Ltd (supra)* it has been held as follows:

> *"While conducting an inquiry into obviousness, hindsight is impermissible and the legal conclusion must be reached on the basis of facts gleaned from the prior art and should not include knowledge gleaned from patent disclosure. Teachings in prior art document have to be considered as a whole. Teachings away from the patent claim are treated as non-obvious. To inquire into obviousness, two fold inquiry is required to be conducted i.e. motivation to select and motivation to modify. Mere structural similarity cannot form the basis for selection of a lead compound in a*

prior art. The legal position is well settled that potent and promising activity in the prior art trumps mere structural similarity. There has to be a teaching, suggestion or motivation in the prior art document in order to modify the lead compound. Besides the primary consideration as noted, the objective indicia of non-obviousness include secondary considerations such as (i) a long-felt need; (ii) failure of others; (iii) industry acclaim; and (iv) unexpected results".

27. The respondent no.2 also erred in not considering the post filing experimental data, written submissions, industrial acclaims and also by refusing to accept any further data during the process of hearing before passing the impugned order. There were no reasons discussed in rejecting the subsequent experimental data. The non-consideration is not only in violation of the provisions of the Act but also contrary to the principles of natural justice.

28. For the above reasons, IPDTA 119 of 2023 stands allowed. The impugned order dated 12 April 2023 is set aside. The above application for patent is remanded to the respondents for consideration afresh after giving an adequate opportunity of hearing to all the parties and upon consideration all the materials on record and the experimental data. It is made clear that all points are left open to be adjudicated upon in accordance with law. The above exercise is to be completed within three months from the date of communication of this order.

(Ravi Krishan Kapur, J.)