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IN THE HIGH COURT OF JUDICATURE AT MADRAS

Judgment reserved on	18.12.2023
Judgment pronounced on	10.07.2024

CORAM

The Hon'ble Mr. Justice **SENTHILKUMAR RAMAMOORTHY**

CMA (PT) No.2 of 2023

Bristol Myers Squibb Company
Route 206 and Province Line Road,
Princeton, New Jersey 08543-4000,
CA 92121, USA .
represented by its constituted attorney/authorised
signatory, Vivek Ratudi ... Appellant

v.

1. Deputy Controller of Patents,
   Patent Office,
   Intellectual Property Building,
   G.S.T. Road, Guindy,
   Chennai – 600032.

2. Indian Pharmaceutical Alliance
   115/116 Ground Floor,
   World Trade Centre, Babar Road,
   Connaught Place, New Delhi-110001 ... Respondents

PRAYER: This Civil Miscellaneous Appeal is filed under Section 117-A of the Patents Act, 1970, to pass an order setting aside the orders

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dated 30 March 2023 passed by the 1st respondent in Indian Patent Application No.5948/CHENP/2014 and pass any other order and/or direction that this Hon'ble Court deems fit and proper in the facts and circumstances of the case.

For Appellant : Ms.Archana Shanker
Mr.K.Premchandar,
Mr.N.C.Vishal,
Mr. Abhishek Arora,
Mr.N.Shrivatsav,
for M/s.Anand & Anand

For Respondent No.1 : Mr.A.R.Sakthivel, SPC

For Respondent No.2 : No appearance

JUDGMENT

Background

The appellant assails an order dated 30 March 2023 by which Patent Application No.5948/CHENP/2014 was rejected by the Indian Patent Office. The said application was the national phase application derived from PCT Application No. PCT/US2013/027648. The claimed invention is titled "N (5S 6S 9R) 5 AMINO 6 (2 3

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DIFLUOROPHENYL) 6 7 8 9 TETRAHYDRO 5H CYCLOHEPTA [B] PYRIDIN 9 YL 4 (2 OXO 2 3 DIHYDRO 1H IMIDAZO [4 5 B] PYRIDIN 1 YL) PIPERIDINE 1 CARBOXYLATE HEMISULPHATE SALT". The base compound is referred to throughout this order as Compound (I) and the claimed invention as the hemisulphate salt of Compound (I). Upon such application being presented before the Indian Patent Office (the IPO) on 04 August 2014 claiming priority from US Application Serial No. 61/603, 598 dated 27 February 2012, the First Examination Report (FER) was issued on 17 July 2018. The appellant responded to the FER on 16 January 2019. A hearing was held on 13 November 2019 and the appellant filed written submissions on 27 November 2019.

2. Upon the appellant requesting for an update in 2020, the appellant was notified of the pre-grant opposition of the second respondent on 17 December 2020. The opposition was filed on the grounds that: claims 1-6 lack novelty in view of anticipation in prior

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art D1; claims 1-6 lack inventive step over prior art documents D1-D4; claims 1-5 are excluded from patent protection under Section 3(d) of the Patents Act, 1970 (the Patents Act); claim 6 is excluded from patent protection under Section 3(e) of the Patents Act; and that there was non-compliance with the requirements of Section 8 of the Patents Act. The appellant filed a reply thereto on 15 March 2021 and a hearing was fixed on 4 January 2023. After the hearing, the appellant filed written submissions on 18 February 2023 and revised submissions on 20 February 2023. The impugned order was issued on 30 March 2023, and the present appeal arises in the said facts and circumstances.

Counsel and their contentions

3. Oral arguments on behalf of the appellant were addressed by Ms.Archana Shanker, learned counsel, assisted by Mr.Prem Chander and Mr.Vishal, learned counsel; on behalf of the first respondent by Mr.A.R.Sakthivel, learned SPC. The second

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respondent remained unrepresented in spite of private notice being served on 21 July 2023 as specified in affidavit of service dated 3 August 2023. The appellant and the first respondent also filed written submissions.

4. Learned counsel for the appellant opened her submissions by pointing out that the monopoly claims are in respect of a hemisulphate salt of Compound (I) and that the international non-proprietary name (INN) given to the substance by the WHO is Rimegepant. With reference to the impugned order, learned counsel pointed out that the objections with regard to both novelty and inventive step were rejected by the first respondent. On account of claim 6 being deleted, she further submitted that the objection with reference to section 3 (e) was rendered moot. In effect, learned counsel submitted that the application was rejected solely by relying on section 3 (d). As regards such rejection, learned counsel submitted that the first respondent failed to appreciate the data provided to

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support the claim that the invention disclosed enhanced bioavailability resulting in enhanced therapeutic efficacy. She submitted that calcitonin gene-related peptides (CGRP), which are naturally occurring amino-acid peptides, bind to receptors and are known to trigger pathophysiologic conditions, such as neurogenic vasodilation, neurogenic inflammation, migraines and other headaches. Therefore, she pointed out that CGRP receptor antagonists are found to be useful in the treatment of the above conditions. When patients take medications such as antacids, proton pump inhibitors and H_2-receptor antagonists, the pH levels in the gastrointestinal (GI) tract increases from the normal range of 1.2 to 1.8 to about 7. This reduces the dissolution rate of CGRP receptor antagonists such as Compound (I) and thereby reduces bioavailability. She further submitted that the claimed invention, which is for a hemisulphate salt of Compound (I), surprisingly reduces the variability, provides consistency in and enhances the bioavailability of Compound (I).

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5. She next referred to the judgment of the Supreme Court in *Novartis AG v. Union of India (Novartis), MANU/SC/0281/2013; 2013 SCC OnLine SC 271*. By referring to paragraphs 165-166 of the SCC OnLine Report, she submitted that the Supreme Court merely held that increased bioavailability alone does not necessarily lead to the enhancement of therapeutic efficacy, and that whether or not an increase in bioavailability leads to an enhancement of therapeutic efficacy in a given case must be specifically claimed and established by research data. On the facts of that case, the Supreme Court rejected the contention based on enhanced bioavailability by recording the factual conclusion that no material was offered to indicate that the beta crystalline form of Imatinib Mesylate would produce enhanced or superior efficacy in comparison to what could be achieved with Imatinib free base. By contrast, she contended that sufficient data was disclosed in the complete specification of the claimed invention to substantiate that enhanced bioavailability

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resulted in enhanced therapeutic efficacy.

6. In this connection, she also referred to the judgment of the Delhi High Court in *Novartis AG v. Natco Pharma Limited(Natco Pharma), Judgment dated 13 December 2021*, particularly paragraphs 14.1.5, 14.2.1, 14.2.7, 14.2.12 and 14.2.13, to contend that the Delhi High Court explained the judgment in *Novartis* and held that it does not exclude patent protection in respect of new forms of a substance exhibiting enhanced bioavailability. She also relied on an article titled "*Drug-Like Property Concepts in Pharmaceutical Design" by Li Di, Edward H. Kerns and Guy T. Carter, 2009 Bentham Science Publishers Ltd.* to emphasize the importance of pharmacokinetics, especially solubility. By also relying on an article titled "*Bio-availability and drug delivery systems: clinical perspective" by AD Bhatt, AB Vaidya, 1992, Volume 38, Issue 3, Journal of Postgraduate Medicine,* she contended that the therapeutic efficacy of a drug is not simply a function of its intrinsic pharmacological activity, and that the path taken by the drug from the site of administration to the site of action is an

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important determinant. Consequently, she submitted that the impugned order is liable to be set aside and that the application should be directed to proceed to grant.

7. These contentions were countered by learned SPC. He commenced his submissions by pointing out that the claims relate to a new form of a known substance, i.e. a hemisulphate salt of the known substance, Compound (I). By pointing out that any claim for a new form of a known substance, especially a pharmaceutical substance, is required to satisfy the requirements of Section 3 (d), he contended that the appellant failed to pass through the filter built into the above mentioned provision. By relying on the judgment of the Supreme Court in *Novartis*, learned counsel pointed out that the Supreme Court held that only enhanced therapeutic efficacy satisfies the requirements of patent eligibility if the claim is in respect of a new form of a known pharmaceutical substance. He further submitted that since enhanced therapeutic efficacy is the only

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measure of enhanced efficacy, increased bioavailability is insufficient unless it is shown to result in enhanced therapeutic efficacy. He concluded his submissions by contending that the appellant completely failed to establish that the enhanced bioavailability resulted in enhanced therapeutic efficacy. As a corollary, he submitted that the claimed invention fails to meet the standards prescribed by the Supreme Court in *Novartis* for the grant of patent to a new form of a pharmaceutical substance.

8. By way of rejoinder, learned counsel for the appellant submitted that bioavailability is not an inherent property of the hemisulphate salt, and that, in *Novartis*, the patent applicant failed before the Supreme Court because it did not provide data with regard to bioavailability and its impact on therapeutic efficacy. By contrast, she contended that the appellant provided data of both *in vitro* and *in vivo* studies, including a solid-state stability study. By relying on internal pages 30 to 42 of the complete specification, she

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contended that the bioavailability of the hemisulphate salt was demonstrated through *in vivo* data to be about 34.73% greater than that of the free base of Compound (I). She pointed out that the C_{max} value, which is the maximum serum concentration that a drug achieves in the body, was only 245 ng/mL in the free base form, whereas it was 2596 ng/mL for the hemisulphate salt. Likewise, she submitted that the blood plasma concentration of the active pharmaceutical ingredient (API) over time (0-24 hours), which is measured by a parameter called area under the curve (AUC), was found to be 12473 ng-h/mL for the hemisulphate salt versus 1762 ng-h/mL for the free base. Hence, she concluded her submissions by contending that the claimed invention passes the exemption filter specified in section 3 (d) of the Patents Act.

Discussion, analysis and conclusions

9. I begin the discussion by examining the conclusions in the impugned order on the objections raised by the second respondent.

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The objection on the ground of lack of novelty was disposed of by recording, in relevant part, as follows in paragraph 3.3 of the impugned order:

> *".... D1 does not specifically disclose the hemisulphate salt of Compound (I). Therefore, the opponent failed to establish the ground of opposition under section 25 (1) (b) of the Patents Act."*

The objection on the ground of lack of inventive step was dealt with and disposed of by recording, in relevant part, as follows in paragraph 3.4 of the impugned order:

> *".... The cited documents D1-D4 either alone or in combination, neither teaches nor suggests hemisulphate salt of compound (I). Further, the hemisulphate salt of compound (I) shows low hygroscopicity, stable crystalline form or hydration state in response to changes in relative humidity and/or temperature and enhanced bioavailability. Therefore, the opponent failed to establish the ground of opposition under section 25 (1) (e)."*

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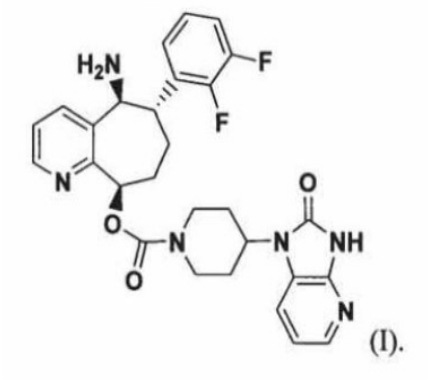
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The above extracts disclose that both these objections were rejected. After doing so, the objection on the basis of Section 3(d) was dealt with. I propose to deal with this objection next.

Exclusion under Section 3(d)

10. In order to test the applicability of Section 3(d), it is necessary to examine the nature of the claims. The amended claims submitted by the appellant along with its written submissions (current claims) before the IPO are as follows:

"1. A hemisulphate salt of compound (I):



(I).

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2. The hemisulphate salt of compound (I) as claimed in claim 1, wherein said salt of Compound (I) is crystalline.

3.The hemisulphate salt of compound (I) as claimed in claim 2, wherein said salt of Compound (I) is sesquihydrate.

4.The hemisulphate salt of compound (I) as claimed in claim 3, wherein said salt comprises crystalline Form H1.5-1.

5.The hemisulphate salt of compound (I) as claimed in claim 4, wherein said Form H1.5-1 is characterized by one or more of the following:

a) unit cell parameters substantially equal to the following:

Cell dimensions: a=10.92 Å

b=33.04 Å

c= 7.90 Å

alpha =90 degrees

beta =90 degrees

gamma=90 degrees

Space group: $P2_12_12$

Molecules of Compound (I)/asymmetric unit:1

Volume:2851 $Å^3$

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Density (calculated) = 1.423 g/cm³,

wherein measurement of said crystalline form is at a temperature of about 25° C;

b) an observed powder x-ray diffraction pattern substantially in accordance with the pattern shown in Figure 1;

c) a simulated powder x-ray diffraction pattern substantially in accordance with the pattern shown in Figure 1,

d) a powder x-ray diffraction pattern (CuK alpha gamma=1.5418 Å) comprising four or more 2 theta values selected from: 5.4±0.1, 8.6±0.l, 9.7±0.l, 12.4±0.1, 14.9±0.1, 17.6±0.l, 18.1±0.1, 20.5±0.1, 21.4±0.1, and 22.0±0.1, wherein measurement of the crystalline form is at a temperature of about 25°C; and/or

e) a solid state nuclear resonance spectra comprising six or more peaks (delta (ppm) referenced to TMS) selected from: 26.6±0.1, 27.1±0.1, 28.3±0.1, 30.7±0.1, 43.l±0.1, 45.9±O.l, 47.1±0.l, 52.0±0.1, 54.2±0.l, 72.5±0.l, 117.0±0.1, 117.7±0.1, 124.2±0.1, 125.2±0.1,128.3±0.1,130.3±0.1,131.4±0.l,134.l±0.l,140.8±0.1,144.7±0.1,148.7±0.1,149.8±0.1,151.2±0.1,153.4±0.1,155.1±0.1,155.6±0.1,and 156.7±0.1."

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On perusal of the current claims, it is evident that independent claim 1 is in respect of a hemisulphate salt of Compound (I). The appellant admits that Compound (I) is a known substance. Thus, the claim is undoubtedly in respect of a new form of a known substance.

11. Section 3 of the Patents Act deals with exclusions from patent protection and clause (d) thereof deals *inter alia* with new forms of a known substance. Section 3(d) is set out below:

> "***3. What are not inventions.*** *- The following are not inventions within the meaning of this Act,-*
>
> ....
>
> *(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.*

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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****; "(emphasis added).*

12. In *Novozymes v. Assistant Controller of Patents, 2023 (6) CTC 644*, I analysed clause (d) of Section 3 as follows:

"12 ....As is evident from the opening "the following are not inventions" expression, which applies to all clauses [(a) to (p)] of Section 3, the provision incorporates a legal fiction by which claims for patent that fall within the clauses of Section 3 will not qualify as inventions, even if such claims meet the requirements of Section 2(1)(j) of the Patents Act, unless they pass through the exemption filters that are built into some of the clauses therein. The principal clause of Section 3(d) contains about three limbs, which are separated by the disjunctive "or". The three limbs are as under:

(i) The mere discovery of a new form of a known

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substance which does not result in the enhancement of the known efficacy of that substance.

(ii) The mere discovery of any new property or new use for a known substance.

(iii) 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.

While it could be contended that there are four and not three limbs because of the placement of the disjunctive "or " before the phrase "new use for a known substance" in what I labelled above as the second limb, I conclude that the second limb is one limb consisting of two segments because the subject of both segments (i.e. "new property" or "new use") of said limb is "known substance". The break-up of Section 3(d) also reveals that both the first and second limbs deal with and govern claims relating to known substances. While the first limb deals with and governs claims relating to new forms of a known substance, the second deals with and governs new properties or new uses thereof. For the sake of completion, it may be noticed that the third limb

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excludes from patent-eligibility, a mere use of a known process, machine or apparatus. It also provides for an exception if such known process results in a new product or employs at least one new reactant.

15. Thus, it was held in Novartis SC that the amendment of Section 3(d) by the Patents (Amendment) Act, 2005 was primarily and especially intended to deal with pharmaceutical products and agro-chemical products. It does not, however, follow from the above that it only applies to pharmaceutical and agro-chemical substances and not to biochemical substances. It was further held by the Supreme Court that the test of efficacy under Section 3(d) would vary depending on the product under consideration and that, in the context of pharmaceutical products, it means therapeutic efficacy....”

Novartis

13. With this preamble, I turn to the principal issue that arises for determination, i.e. whether the claimed invention is liable to be rejected on the ground that bioavailability cannot be the basis for a

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claim of enhanced efficacy. Both parties referred to the judgment of the Supreme Court in *Novartis.* The first aspect to be considered is whether the Supreme Court concluded in *Novartis* that incremental inventions are shut out by clause (d) of Section 3. Paragraph 168 of the SCC OnLine report contains a categorical answer, and the same is set out below:

> *"168. We have held that the subject product, the beta crystalline form of Imatinib Mesylate, does not qualify the test of Section 3 (d) of the Act but that is not to say that Section 3 (d) bars patent protection for all incremental inventions of chemical and pharmaceutical substances. It will be a grave mistake to read this judgment to mean that section 3 (d) was amended with the intent to undo the fundamental change brought in the patent regime by deletion of Section 5 from the parent Act. That is not said in this judgment."*

It follows from the above extract that the Supreme Court concluded that incremental inventions are restricted but not prohibited under section 3 even with respect to pharmaceutical products. Indeed, the

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only reasonable inference that flows from the judgment is that Section 3(d) is intended to prevent evergreening and to enable genuine incremental inventions. The other conclusions of the Supreme Court in the said judgment also call for close analysis.

14. In *Novartis*, the patent application was in respect of the beta crystalline form of Imatinib Mesylate. The API was admittedly Imatinib in free base form. One of the questions considered by the Supreme Court was whether the non-crystalline form of Imatinib Mesylate was within the scope of the Zimmerman Patent. This question was answered as follows:

> *"135. In light of the discussions made above, we firmly reject the appellant's case that Imatinib Mesylate is a new product and the outcome of an invention beyond the Zimmerman Patent. We hold and find that Imatinib Mesylate is a known substance from the Zimmerman Patent itself. Not only is Imatinib Mesylate known as a substance in the Zimmerman patent, but its pharmacological properties are also*

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known in the Zimmerman Patent and in the article published in Cancer Research journal referred to above. The consequential finding, therefore, is that Imatinib Mesylate does not qualify the test of "invention" as laid down in Section 2 (1) (j) and Section 2 (1) (ja) of the Patents Act 1970."

15. The next issue considered by the Supreme Court was whether the pharmacological properties of Imatinib Mesylate in beta crystalline form are found in Imatinib in free base form. After noticing that the patent application contained a categorical statement that all the indicated inhibitory and pharmacological effects are also found with the free base, the Supreme Court recorded the following leading question:

"142. Now, when all the pharmacological properties of beta crystalline form of Imatinib Mesylate are equally possessed by Imatinib in free base form or its salt, where is the question of the subject product having any enhanced efficacy over the known substance of which it is a new form?"

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16. Thereafter, the Supreme Court took note of the affidavit of Giorgio Pietro Massimini, wherein it was stated that the beta crystalline form of Imatinib Mesylate exhibited 30% improvement in bioavailability as compared to the free base form. In light of the earlier finding that Imatinib Mesylate was within the scope of the Zimmerman Patent, the Supreme Court entered the following finding:

> *"150. That being the position, the appellant was obliged to show the enhanced efficacy of the beta crystalline form of Imatinib Mesylate over Imatinib Mesylate (non-crystalline). There is, however, no material on the subject application or in the supporting affidavits to make any comparison of efficacy, or even solubility, between the beta crystalline form of Imatinib Mesylate and Imatinib Mesylate (non-crystalline)."*

17. The Supreme Court next noticed that the patent applicant made a claim that the beta crystalline form of Imatinib Mesylate has higher solubility, beneficial flow properties, better thermodynamic

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stability and lower hygroscopicity. After concluding that such properties cannot be said to result in enhanced efficacy over the non-crystalline form of Imatinib Mesylate, the Supreme Court examined whether the patent applicant had established enhanced therapeutic efficacy. This question was examined with regard to the claim of increased bioavailability, and the following findings were recorded:

> *"165. This leaves us to consider the issue of increased bioavailability. It is the case of the appellant that the beta crystalline form of Imatinib Mesylate has 30% increased bioavailability as compared to Imatinib in free base form. If the submission of Mr Grover is to be accepted, then bioavailability also falls outside the area of efficacy in case of a medicine. Leaving aside the submission of Mr Grover on the issue, however, the question is, can a bald assertion in regard to increased bioavailability lead to an inference of enhanced therapeutic efficacy? Professor Basheer referred to a report from a commentator on the issue of bioavailability as under:*
>
> *"It is not the intent of a bioavailability study to demonstrate effectiveness, but to determine the rate and*

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extent of absorption. If a drug product is not bioavailable, it cannot be regarded as effective. However a determination that a drug product is bioavailable is not in itself a determination of effectiveness."

166. Thus, even if Mr Grover's submission is not taken into consideration on the question of bioavailability, the position that emerges is that just increased bioavailability alone may not necessarily lead to an enhancement of therapeutic efficacy. Whether or not an increase in bioavailability leads to an enhancement of therapeutic efficacy in any given case must be specifically claimed and established by research data. In this case, there is absolutely nothing on this score apart from the adroit submissions of the counsel. No material has been offered to indicate that the beta crystalline form of Imatinib Mesylate will produce an enhanced or superior efficacy (therapeutic) on molecular basis than what could be achieved with Imatinib freebase in vivo animal model."

18. Before proceeding to crystallize the principles laid down in *Novartis* and evaluate the impact thereof on this case, it is instructive

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to examine the Delhi High Court's judgment dated 24 April 2024 in *Natco Pharma v. Novartis AG and another, FAO(OS)(COMM)178/2021 (Natco Pharma DB)* in which *Novartis* was considered. The appellant relied on *Natco Pharma,* which is the order of a single judge of the Delhi High Court granting an interim injunction restraining Natco Pharma from *inter alia* selling the API *Eltrombopag bis* (ELT-O) on the ground that it *prima facie* infringes suit patent IN 233161. Such suit patent was granted on the basis of enhanced solubility and bioavailability over ELT, which is the free acid. The single judge analysed *Novartis* and concluded that the Supreme Court held therein that increased bioavailability can be an indicator of increased therapeutic efficacy subject to the patent holder establishing that increased bioavailability resulted in increased therapeutic efficacy (see paragraph 33.2). The single judge also held that sufficient data was provided by Novartis to succeed. When the matter was carried in appeal in *Natco Pharma DB,* the Division Bench reversed and held as follows:

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> *"86. Enhanced bioavailability is not synonymous with higher therapeutic efficacy. As noted above, in Novartis v. UoI, the Supreme Court had – without going into the question whether increased bioavailability by itself would lead to an enhancement of therapeutic efficacy, expressly held that, if such a claim is made, the same would require to be established by research and data.*
>
> *87. The assumption that enhanced bioavailability necessarily leads to enhanced therapeutic efficacy is too broad an assumption. It is desirable to have optimal pharmacokinetic parameters. In cases where a formulation has side effects, a lower bioavailability may be more beneficial.*
>
> *88. In the present case, the applicant (predecessor in interest of Novartis AG) had made no claim for enhanced therapeutic efficacy in its patent application; the only added advantage claimed in respect of ELT-O was "enhanced solubility and bioavailability."*

I now revert to the facts of the case at hand to understand the impact of *Novartis* thereon.

Bioavailability and therapeutic efficacy

19. In the factual context of the claims set out at paragraph 10

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supra, the appellant contended that the complete specification contains sufficient disclosure, including supporting experimental data, of enhanced bioavailability and the resulting enhanced efficacy. The appellant pointed out that bioavailability is dependent on factors such as solubility of the drug in the GI tract, the stability of the drug, drug absorption, with or without food, including when used along with other medications. As regards the problem resolved by the claimed invention, the appellant stated that the dissolution rate of Compound (I) was dependent on the pH in the GI tract. The pH, in turn, was dependent on whether antacids, proton pump inhibitors and H_2 receptor antagonists are used by the patient. The appellant pointed out that the use of Compound (I) with H_2 receptor antagonists resulted in lower dissolution rate of the API. By contrast, the hemisulphate salt of the compound reduced the variation in bioavailability and thereby enabled consistency in dosage of the API. This discussion clearly leads to the meaning of bioavailability and, more importantly, its relationship with therapeutic efficacy.

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20. Bioavailability is defined in more than one manner in medical literature, and it is instructive to set out a couple of such definitions. In an article titled "*Drug Bioavailability", Gary Price and Deven A.Patel, 2024, StatPearls Publishing LLC,* it is defined as under:

> *"Bioavailability refers to the extent a substance or drug becomes completely available to its intended biological destination(s). More accurately, bioavailability is a measure of the rate and fraction of the initial dose of a drug that successfully reaches either; the site of action or the bodily fluid domain from which the drug's intended targets have unimpeded access."*

Another definition and explanation from an article titled "*Bioavailability Importance and Implications in Pharmacology", by Michele Philip, Journal of Pharmacology Reports, 7:178,* is as under:

> *" Bioavailability refers to the extent and rate at which a drug or any active ingredient becomes available at the site of action in the body. It is a crucial parameter in pharmacology and pharmaceutical sciences as it*

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determines the efficacy and therapeutic effect of a drug. Understanding the bioavailability of a drug is essential for proper dosing, formulation development, and optimizing therapeutic outcomes."

Given that bioavailability refers to the extent and rate at which the API in a formulation reaches the intended site of action in the body, one of the factors impacting bioavailability is the mode of administration. Drugs may be administered *inter alia* through the following modes: oral, intramuscular, intravenous, transdermal and inhalation. By way of illustration, when tablets or capsules are swallowed, they pass through the GI tract before reaching the circulatory system. Consequently, the GI tract environment would have an impact. By contrast, when administered intravenously, the drug reaches the blood stream directly. Apart from the mode of administration, distribution, metabolism and clearance/excretion also play a role in bioavailability. Thus, bioavailability is a pharmacokinetic parameter, i.e. it deals with the movement of the drug through the body and the impact of the body on the drug.

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21. Bioavailability is measured on different benchmarks. One of the most effective methods is to determine the blood plasma concentration of the API over time, which measure is called area under the plasma concentration curve or AUC. The other is maximum serum concentration (C_{max}) that a drug achieves in a specified area of the body. In the complete specification, the appellant set out details of a comparative study undertaken *in vivo* on humans to whom Compound (I) was administered after pre-treatment with 40 mg of famotidine (a H_2 receptor antagonist) and those to whom only Compound (I) was administered. The results of this study are set out in Table 7 thereof. Both on the parameters of AUC and C_{max}, the values fell sharply for those pre-treated with 40 mg of famotidine, thereby indicating the sharp reduction in bioavailability upon rise in pH levels.

22. The complete specification also contains details of another

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study wherein Compound (I) or the hemi-sulphate salt, as the case may be, was administered to dogs pre-treated with famotidine or pentagastrin. The results of this study, which are set out in Table 8, are as under:

Table 8

Pharmacokinetic Parameters for Dosing in Dogs of 150 mg of Compound (I) as Hemisulfate salt or Free base.

	C_{max} (ng/mL)		T_{max} (h)	AUC_{0-24hr} (ng·h/mL)		BA (%)		CV (%)
	Mean	Std Dev		Mean	Std Dev	Mean	Std Dev	
Compound (I) + pentagastrin	8156	4423	0.75	38796	15407	100	-	39.71
Compound (I) + famotidine	245	95	2	1762	392	4.54	1.01	22.23
Example 1 + famotidine	2596	409	1	13473	2098	34.73	5.41	15.57

Table 8 indicates that the claimed invention exhibits 34.73% bioavailability, when administered to dogs pre-treated with famotidine, in comparison to Compound (I), which exhibits 4.54% bioavailability when subjected to the same treatment protocol. As regards AUC, the claimed invention exhibited AUC of 13,473 ng/ml

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versus 1762 ng/mL for Compound (I). Likewise, as regards the C_{max} value, such value is 2596 ng/mL for the claimed invention versus 245 ng/ml for Compound (I). This leads to the question as to how this data was dealt with in the impugned order.

23. While dealing with the question of patentability, the following conclusions were recorded in the impugned order:

> *"The data submitted by the applicant in page 38, table 8 of the present application and in the written submissions is only increased bioavailability of the hemisulphate salt of compound I versus compound I freebase and no data has been provided in the complete specification as well as the applicant's submissions that the increased bioavailability results in increased therapeutic efficacy. The increased bioavailability cannot be considered as therapeutic efficacy."*
>
> *"In view of above discussions and the settled position in law as stated above, the present claimed compound hemisulphate salt of compound I is considered to be the*

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same substance as it does not differ significantly in properties with regard to efficacy over the prior art and thus the present claims 1 to 5 on record falls under section 3 (d) of the Patents Act. The applicant deleted claim 6 therefore, objection under section 3 (e) stands moot. Therefore, the opposition filed by the opponent under section 25 (1) (f) is stands maintained."

24. In effect, the first respondent concluded that there was evidence of increased bioavailability in the data provided in Table 8 but no data that the increased bioavailability resulted in increased therapeutic efficacy. Bioavailability being a pharmacokinetic property and not a pharmacodynamic (i.e. effect of drug on body) property, it is not even theoretically possible to establish that increased bioavailability *per se* enhances intrinsic pharmacological activity. As a corollary, a monopoly claim for increased therapeutic efficacy only on account of increased bioavailability would be untenable. The Supreme Court judgment should not, in my view, be construed as requiring either the impossible or the untenable.

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25. On closely examining the judgment of the Supreme Court in *Novartis,* it is evident that the Court held that a claim for enhanced therapeutic efficacy cannot be accepted merely on the basis of an assertion of enhanced bioavailability. It was further held that bioavailability is essential for therapeutic efficacy but bioavailability *per se* does not establish therapeutic efficacy. The following lines "*Whether or not an increase in bioavailability leads to an enhancement of therapeutic efficacy in any given case must be specifically claimed and established by research data*", from *Novartis* should be understood as requiring that a patent applicant, who makes the application on the basis of enhanced bioavailability, should establish through data that administration of a specific quantity of the claimed new form of a known substance by a particular mode has greater therapeutic efficacy in view of the greater bioavailability thereof *vis-a-vis* administration of an equal quantity of the base compound by the

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same mode. Such applicant could also show that the greater bioavailability enables administration of lower doses thereby lowering toxicity or other adverse effects, which would impair therapeutic efficacy. In fact, such claim is made in the written submissions of the appellant in course of patent prosecution. In paragraph 87 of *Natco Pharma DB,* the Delhi High Court highlighted that it is possible that higher bioavailability could result in greater toxicity or other side effects.

26. Indeed, in *Novartis,* the Supreme Court noticed the contention of Mr.Grover that therapeutic efficacy can only be established on the basis of pharmacodynamic properties, but did not record any finding on such contention. Instead, the Supreme Court left the door open for incremental inventions based on enhanced bioavailability subject to the requirements set out above. While examining whether enhanced bioavailability results in enhanced therapeutic efficacy, it also becomes necessary to be mindful of the

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challenges. For an illuminating discussion, it is profitable to refer to the article "*The "Efficacy" of Indian Patent Law: Ironing out the Creases in Section 3(d), late Professor Shamnad Basheer and T.Prashanth Reddy, (2008) 5:2 Script-ed.*" Whether the appellant fulfilled the above requirements warrants consideration in this context.

27. At internal page 15 of the complete specification, the appellant indicates that the claimed invention envisages administering therapeutically effective quantities by stating as under:

> *"Compounds are generally given as pharmaceutical compositions comprised of a therapeutically effective amount of the hemisulphate salt of Compound (I), and a pharmaceutically acceptable carrier, and may contain conventional excipients. A therapeutically effective amount is the amount needed to provide a meaningful patient benefit as determined by practitioners in that art...."*

Against this backdrop, Table 8 discloses that 150 mg of Compound (I) or 150 mg of the hemisulphate salt of Compound (I), as the case may

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be, were administered to dogs pre-treated with famotidine (a H_2 receptor antagonist that raises the pH levels in the GI tract) and that the bioavailability of the hemisulphate salt is 34.73%, whereas that of Compound (I) is only 4.54%. As regards therapeutic efficacy, the complete specification discloses that CGRP is a naturally occurring amino acid and that CGRP receptor activation is implicated in pathophysiologic conditions, such as neurogenic vasodilation, neurogenic inflammation, migraine and the like. After reciting that Compound (I) is suitable as a CGRP receptor antagonist, the following recital is set out with regard to the therapeutic efficacy of the hemisulphate salt at internal page 15 of the complete specification:

> *"The hemisulphate salt of Compound (I) inhibits the CGRP receptor. As such, the hemisulphate salt of Compound (I) is useful for treating conditions or disorders associated with aberrant CGRP levels or where modulating CGRP levels may have therapeutic benefit."*

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28. These aspects were not considered by the first respondent on account of the conclusions drawn with regard to Section 3(d) purportedly on the basis of *Novartis*. As stated earlier, enhanced therapeutic efficacy as regards a claim based on bioavailability can only be tested on the criteria specified in paragraph 25 *supra* and not on enhanced intrinsic pharmacological activity per unit of API. Therefore, interference with the impugned order is warranted. On closely examining the complete specification, I find that all material aspects may be examined within the framework of the complete specification, albeit with modifications, if any, in terms of Section 59 of the Patents Act. A remand is, however, necessary for this purpose.

29. For reasons set out above, CMA (PT)/2/2023 is disposed of on the following terms without any order as to costs:

(i) The order dated 30 March 2023 is set aside and the matter is remanded for reconsideration.

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(ii) In order to preclude the possibility of pre-determination, an officer other than the officer who issued the order impugned herein shall undertake reconsideration.

(iii) Such reconsideration shall be undertaken by taking into account observations set out in this judgment for the limited purpose of examining whether the enhanced bioavailability of the hemisulphate salt of Compound (I) is significant and whether it has the effect of enhancing therapeutic efficacy, albeit not by way of enhanced intrinsic pharmacological activity per unit of API.

(iv) Amendments, if any, to the complete specification or claims shall be permitted if within the framework of the complete specification.

(v) A fresh order on Indian Patent Application No.5948/CHENP/2014 shall be issued within six months from the date of receipt of a copy of this order.

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CMA(PT)/2/2023

10.07.2024

Index : Yes / No
Internet : Yes / No
Neutral Citation : Yes/ No
kal

To

The Controller of Patents,
Patent Office,
Intellectual Property Building,
G.S.T. Road, Guindy,
Chennai – 600032.

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SENTHILKUMAR RAMAMOORTHY J.

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Pre-delivery judgment made in
CMA (PT) No.2 of 2023

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CMA(PT)No.2/2023 and C.M.P.No.14512 of 2023

SENTHILKUMAR RAMAMOORTHY.J,

The matter is listed today upon being mentioned by learned counsel for the appellant.

2. Based on the hearing notice, learned counsel for the appellant states that the officer hearing the matter is endeavouring to expand the scope of proceedings.

3. On instructions, Mr.A.R.Sakthivel, learned SPC, submits that the scope of proceedings would be confined to rejection under Section 3(d) of the Patents Act, 1970. The said statement is recorded and these proceedings are closed.

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19.09.2024

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