IN THE HIGH COURT OF DELHI AT NEW DELHI

% Judgment delivered on: 21.10.2019

\+ **W.P.(C) 7585/2016 & CM Nos. 31253/2016, 32248/2016, 41210/2016, 41251/2016, 5677/2018, 27659/2018, 28204/2018, 47154/2018, 1301/2019, 8471/2019 & 13702/2016**

BOEHRINGER INGELHEIM INDIA PVT. LTD. ..... Petitioner

versus

DRUGS CONTROLLER GENERAL OF INDIA & ANR ..... Respondents

Advocates who appeared in this case:

For the Petitioner: Mr Sudhir Chandra, Sr. Advocate with Mr Sanjay Kumar, Ms Arpita Sawhney and Mr Arun Kumar Jana, Advocates.

For the Respondents: Mr Kirtiman Singh, CGSC with Mr Prateek Dhanda and Mr Waize Ali Noor, Advocates for R-1.

Mr Abhinav Vasisht, Sr. Advocate with Ms Shyel Trehan and Mr Aman Shukla, Advocates for R-2.

CORAM
HON'BLE MR JUSTICE VIBHU BAKHRU

JUDGMENT

VIBHU BAKHRU, J

1. The petitioner has filed the present petition, *inter alia,* praying for revocation of the marketing approval granted to respondent no.2 (M/s Gennova Biopharmaceutical Pvt. Ltd.) for its drug 'Tenectase', used for the treatment of Acute Ischemic Stroke (AIS). The petitioner also

contends that introduction of a biosimilar (TNK-t-PA) for AIS in the Indian market, is illegal.

2. The petitioner claims that the drug manufactured by respondent no. 2 – Tenectase – is a biosimilar of the drug Tenecteplase (TNK-t-PA), which is manufactured by the petitioner and claims that such manufacture of a biosimilar drug without reference to the innovator drug is impermissible. Respondent no. 2 contends that the marketing approval granted to its drug 'Tenectase', has been granted as a "New Drug" under the provisions of the Drugs and Cosmetics Act, 1940 (hereafter 'the Act') and the Drug and Cosmetic Rules, 1945 (hereafter 'the Rules'). It also disputes that 'Tenectase' is a biosimilar of 'Tenecteplase' (TNK-t-PA).

3. The principal controversy involved in the present petition is whether the marketing approval granted to respondent no. 2 for the said drug (Tenectase) is in accordance with the Act and the Rules. The petitioner claims that the marketing approval has been granted without respondent no.2 conducting the necessary trials as specified under Schedule 'Y' of the Rules. And, the same is mandatory. This is disputed by the respondents. It is their contention that the approval has been granted after conduct of the trials, as considered appropriate and the same is in compliance with the Rules.

4. The aforesaid controversy arises in the following context.

Factual Background

5. The petitioner is a subsidiary of Boehringer Ingelheim Auslandsbeteiligungs GmbH, a global pharmaceutical company. One of the products of the petitioner is 'Metalyse' (Tenecteplase – hereafter 'TNK-t-PA'), which is a fibrin clot dissolving drug indicated for the thrombolytic treatment of Acute Myocardial Infarction (AMI). It is stated that the efficacy of Metalyse for the treatment of AMI has been demonstrated in approximately twenty thousand patients treated with TNK-t-PA in monitored clinical studies. The European Union granted authorization, by a centralised procedure, for Boehringer Ingelheim's Metalyse on 23.02.2001. Boehringer Ingelheim holds the Marketing Authorization in all countries except in the USA, Canada and Japan. Metalyse is currently authorized in eighty-nine countries and is marketed in eighty-six of those countries.

6. TNK-t-PA is a 'biologic', co-marketed by Boehringer Ingelheim Auslandsbeteiligungs GmbH (the parent company of the petitioner). A biologic is a biological product derived from a living cell, mostly from an animal or a micro-organism like bacteria. The parent company of the petitioner is the innovator of the biologic 'TNK-t-PA', which is marketed as 'Metalyse', for the indication of AMI, as duly approved by the Drugs Controller General of India (hereafter 'DCGI'). 'Metalyse' has been approved for AMI only; it has not been approved for AIS.

7. Respondent No.2 (M/s Gennova Biopharmaceutical Pvt. Ltd) is a biotechnology company and is one of the subsidiaries of Emcure

Pharmaceuticals Limited, which develops and delivers advance specialty biopharmaceutical products.

8. Respondent no.2 states that it also markets a drug called 'Elaxim', which is used for the treatment of AMI. The active ingredient being used in 'Elaxim' is TNK-t-PA. The petitioner also markets a drug for AIS called 'Actilyse'.

9. As per the information available in the public domain, the US FDA approved 'TNK-t-PA' for the treatment of AMI. The innovator of the said drug is stated to be M/s Genentech Inc.

10. On 20.12.2005, the petitioner applied for approval to import and market Tenecteplase for the treatment of AMI under the brand name 'Metalyse', in the dosage strength of 0.5 mg. Subsequently, on 06.02.2007, the DCGI approved the aforesaid drug for import and marketing in India.

11. On 06.01.2006, respondent no.2 was granted permission to carry out human clinical trials of TNK-t-PA (Tenecteplase) by the Government of India, Ministry of Science and Technology, Department of Biotechnology.

12. On 07.08.2006, respondent no. 2 applied for the approval to manufacture and market a product based on the similar biologic drug substance of Tenecteplase. Approval was obtained to manufacture and market 'Elaxim 0.5 mg' for the treatment of AMI.

13. Respondent no.2 has been marketing 'Elaxim' for the treatment of AMI since 2007. On 18.05.2007, DCGI also granted a No-Objection Certificate (NOC) to respondent no.2 for manufacturing and marketing Tenecteplase for additional lower strength packs of 40mg/30mg/20mg.

14. On 03.12.2008, respondent no.2 applied for a NOC to conduct clinical trials to assess the safety and efficacy of Tenecteplase in AIS in the dosage strength of 0.1 mg and 0.2 mg, on fifty patients. On 29.01.2009, respondent no.2 submitted a clinical study protocol to DCGI to assess the efficacy and tolerability of Tenecteplase in AIS for phase II/III trials of dosage strength of 0.1 mg/kg and 0.2 mg/kg.

15. DCGI called upon respondent no. 2 to submit various other documents and meet other requirements. Upon fulfillment of the same, on 27.02.2009, a NOC was issued to respondent no.2 to conduct the clinical trials. On 24.06.2009, the clinical trials to assess the efficacy and safety of Teneceteplase in AIS was registered with the Clinical Trial Registry of India (CTRI) by respondent no.2.

16. On 08.10.2010, respondent no.2 submitted its clinical trial results on fifty patients (that is, 0.1 mg on twenty patients and 0.2 mg on thirty patients), vide its report to the DCGI. This was done pursuant to the aforesaid NOC dated 27.02.2009.

17. On 15.06.2011, the report as submitted by respondent no.2 was examined by the Expert Committee and it was recommended that the manufacturer needs to provide data for clinical trial conducted on a minimum of one hundred subjects.

18. On 19.08.2011, DCGI pursuant to the analysis of the data submitted on 08.10.2010, directed respondent no.2 to conduct a follow up study in fifty additional patients to meet the regulatory requirements.

19. On 17.10.2011, respondent no.2 submitted its protocol for the conduct of clinical trials on fifty additional subjects of ischemic stroke patients and requested permission for the same.

20. On 05.12.2013, respondent no.1 granted a NOC to respondent no. 2 to carry out another clinical trial vide Protocol No. GBL/TNK-TPA/AIS/2012/001 version dated 10.05.2013. The said NOC also mentioned the investigators under whose permission the trial was to be conducted. By a further communication dated 22.10.2014, certain additional sites and investigators were approved for the purposes of the clinical trial. The said trial was registered with CTRI on 19.02.2015 by respondent no.2.

21. On 13.07.2016, respondent no. 2 submitted its clinical trial report to the DCGI, after conducting trial on fifty-four additional patients at a dosage strength of 0.2mg/kg.

22. On 18.07.2016, the 22nd Subject Expert Committee (SEC - Neurology and Psychiatry) – in light of the representation made by respondent no. 2 – recommended the approval of marketing authorization of Tenecteplase for AIS within three hours of stroke initiation. However, the Committee also recommended that respondent no.2 conduct active post marketing surveillance for safety evaluation in one thousand patients as per the ICH guidelines. In addition, the

Committee directed that the data after completion of the first five hundred patients be submitted to the DCGI, for evaluation by the Committee.

23. In view of the recommendations made by the 22nd SEC (Neurology and Psychiatry), on 28.07.2016, DCGI granted the approval of additional indication of Tenecteplase Injection 20 mg for AIS, to respondent no. 2.

24. The petitioner has impugned the aforementioned marketing approval by way of the present petition.

Submissions

25. Mr Chandra, learned senior counsel appearing for the petitioner contended that Tenectase is a biosimilar product and has been developed illegally without reference to an innovator drug or the biologic as is required under the 'Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorisation in India' (hereafter 'the Similar Biologics Guidelines') as issued by the Department of Biotechnology, Government of India and Central Drugs Standard Control Organization (CDSCO). He contended that in terms of the said Guidelines, it is necessary to have a biologic as a comparator. And, it is necessary to demonstrate the drug in question is similar to the reference biologic.

26. He submitted that although the extent of pre-clinical and clinical evaluation for a similar biologic is less than that required for a reference

biologic; nonetheless, it is essential that the similar biologic also meets the acceptable level of safety, efficacy and quality.

27. Mr Chandra countered the case of the respondents that Tenectase could be considered as a "New Drug". He submitted that respondent no. 2 could not have possibly developed a new drug and in case it claims to do so, it would be necessary for respondent no.2 to conduct all pre-clinical and clinical trials as stipulated in Schedule 'Y' of the Rules. He submitted that since respondent no. 2 had not conducted all the phases of the trials, the marketing approval granted to respondent no.2 for the drug Tenectase, ought to be revoked.

28. He earnestly contended that grant of permission to conduct abbreviated trials was illegal and without any jurisdiction. He referred to an Office Order dated 03.07.2014 issued by the DCGI and contended that in terms of the said Office Order, waiver of clinical trials for 'New Drugs' could be considered only in cases of national emergency and extreme emergency and only in cases where the drug had been approved outside India. He submitted that since these conditions were not satisfied in this case, the approval for abbreviated clinical trials was not justified.

29. Next, he submitted that respondent no.2 could not be exempted from conducting Phase-I and II trials, as required under Scheduled 'Y' of the Rules, could not be done away on the ground that such trials had been undertaken for the drug Tenecteplase. He submitted that the said trials were conducted for the indication of AMI and not for AIS. He

submitted that merely because trials were conducted for a higher dosage in AMI patients, the same would not automatically exclude the requirement of conducting trials for lower dosages and ASI patient. He further emphasized that the risk of intracranial bleeding was six times higher in case of a patient suffering from a stroke than in case of a heart attack. Next, he contended that even Phase-III trials have not been conducted. Such trials were required to be conducted in one hundred patients, but trials for dosage of 0.2 mg had been conducted only in ninety-one patients. It was further submitted on behalf of the petitioner that Tenecteplase had not been approved for the indication of AIS anywhere in the word and therefore, Phase-III data was required to be obtained on a larger population of patients.

30. Mr Kirtiman Singh, learned counsel appearing for the DCGI and Mr Abhinav Vasisht, learned Senior Counsel appearing for respondent no.2 countered the submissions made on behalf of the petitioner.

31. At the outset, they submitted that the petitioner has abused the process of this Court. They contended that the petitioner had caused a similar petition – W.P.(C) 7357/2016 – to be filed by one Dr Deep Dass, wherein he had sought reliefs similar to those sought by way of this petition. They pointed out that one of the principal documents relied upon in the said petition indicated that it was generated at the office of the petitioner. This was obvious because the footer of the said document contained the following link : *eu.boehringer.com/users/mum/users/kedars/Desktop/PIL/Indian%20GCP.html*. This indicated that that the document was generated from the

computer system of one Mr Kedar Suvarnapathaki, Head of Regulatory Affairs and IP of the petitioner. The link also indicated that the said document was generated for the purposes of a Public Interest Litigation (PIL). The said petition was listed on 23.08.2016 and on the said date, it was directed to be listed before the concerned Roster Bench which was hearing PIL matters. It was further listed on 24.08.2016 before the concerned Roster Bench. On that day, the *ad-interim* relief as sought was not granted to the petitioner therein (Dr Deep Das). The present petition was filed five days later for seeking similar reliefs without disclosing the filing of the earlier petition.

32. It is stated that in the proceedings pertaining to the writ petition filed by Dr Deep Das, respondent no.2 had filed an application under Section 340 of the CrPC being Crl. M. A. 13461/2016. In the reply filed to the said application, Dr Deep Das had affirmed that "*the Petitioner in filing the writ petition has no relationship, whatsoever, with any entity including Boehringer*". This statement is found to be incorrect since it was later revealed that Dr Deep Das had been paid an honorarium by the petitioner. Dr Deep Das had thereafter withdrawn that writ petition.

33. It was contended on behalf of the respondents that the present litigation is motivated as the petitioner is a competitor of respondent no.2 and is also engaged in marketing a drug for treatment of AIS, namely, Actilyse and the present petition has been filed solely to thwart any competition by respondent no.2.

34. It was next contended that the drug Tenectase was not approved as a similar biologic but as a new drug and therefore, there was no question of respondent no.2 following the "guidelines on similar biologics". The respondents contended that there was no requirement for respondent no.2 to establish similarity with any reference biologic for seeking approval of 'Tenectase' as a new drug.

35. The respondents also countered the contention that respondent no.2 had not followed the required protocol and/or submitted the necessary data as required for seeking approval of its drug Tenectase. It was submitted that the requisite trials as required to be conducted by DCGI were, in fact, conducted.

Reasons & Conclusion

36. This court finds merit in the contention that the petitioner had caused Dr Deep Das to file a PIL and had filed the present petition only after Dr Deep Das had failed to secure any interim order from this Court. There is no dispute that Dr Deep Das had relied upon on a document captioned – Good Clinical Practices For Clinical Research In India – issued by CDSCO, Ministry of Health and Family Welfare, Government of India and the printout of the said document indicates that the same had emanated from the computer system of the petitioner. The footer of the printout of the said document (annexed as 'Annexure -G' to the writ petition filed by Dr Deep Das) indicates that the same was retained as a soft copy on the computer system of the petitioner. It also appears that the same was one of the documents retained on the

computer system for the purposes of PIL, as is evident from the link at the footer of the printout of the document in question.

37. It is also clear that the petitioner and respondent no.2 are competitors, inasmuch as, both the entities are manufacturing and marketing drugs to be used for treatment of AIS. In view of the above there is much merit in the contention that exercise of any discretion in favour of the petitioner is not warranted. Nonetheless, since the petitioner has raised an issue with regard to grant of approval contrary to law, this Court considers it apposite to examine that question.

38. The principal question to be addressed in the present case is whether the marketing approval granted to respondent no.2 for its drug Tenectase to be used for treatment of AIS, is contrary to law.

39. Admittedly, respondent no.2 has not secured the approval on the basis that the said drug is a biosimilar. In terms of the Guidelines on Similar Biologics, similar biologics can be developed and established by assessing similarity with regard to a reference biologic. Undisputedly, in the present case, respondent no.2 has not sought the approval of Tenectase on account of bio similarity with any other biologic but as a 'new drug'. In the circumstances, the limited question to be examined is whether respondent no.2 has been granted the approval for Tenecteplase as a new drug in accordance with the Rules.

40. Rule 122E of the Rules defines the expression "new drug" and is set out below:-

"**122E Definition of new drug**. —For the purpose of this part, new drug shall mean and include—

[(a) A drug, as defined in the Act including bulk drugs substance which has not been used in the country to any significant extent under the conditions prescribed, recommended or suggested in the labelling thereof and has not been recognised as effective and safe by the licensing authority mentioned under rule 21 for the proposed claims: Provided that the limited use, if any, has been with the permission of the licensing authority.]

(b) A drug already approved by the licensing authority mentioned in rule 21 for certain claims, which is now proposed to be marketed with modified or new claims, namely, indications, dosage, dosage form (including sustained release dosage form) and route of administration.

(c) A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz ., indications dosage, dosage form (including sustained release dosage form) and route of administration. (See items (b) and (c) of Appendix VI to Schedule Y).

Explanation. —For the purpose of this rule—

[(i) all vaccines and Recombinant DNA (r-DNA) derived drugs shall be new drugs unless certified otherwise by the Licensing Authority under rule 21;]

(ii) a new drug shall continue to be considered as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia whichever is earlier.]]"

41. It is respondent no.2's case that Tenectase contains the active ingredient 'Tenecteplase' which has already been approved for the treatment of AMI. Since the said drug was proposed to be marketed with a modified dosage for the indication of ASI, the same would qualify as a new drug under Rule 122E (b) of the Rules.

42. There is no dispute that respondent No.2 was granted the approval to manufacture Tenecteplase (TNK-t-PA) for the treatment of AMI by DCGI on 07.08.2006. The said drug has been marketed for the aforesaid indication by respondent no.2 under the name 'Elaxim'. Respondent no.2 proposed to use the same drug in a modified dosage form for treatment of AIS. A plain reading of Rule 122E(b) of the Rules indicates that an approved drug, which is proposed to be used for new claims, including indications and dosages, would qualify as a 'new drug'. Thus, TNK-t-PA in a modified dosage for the indication of ASI would qualify as a new drug in terms of Rule 122E(b) of the Rules. In view of the above, in order to secure approval for manufacture of the said drug, respondent no.2 was required to seek approval from the Licensing Authority in terms of Rule 122B of the Rules. Rule 122B of the Rules is set out below:-

> "**122B. Application for approval to manufacture new drug** :(1) (a) No new drug shall be manufactured for sale unless it is approved by the Licensing Authority as defined in clause (b) of rule 21.
>
> (b) An application for grant of approval to manufacture the new drug and its formulations shall be made in Form 44 to the Licensing Authority as defined in clause (b) of rule 21 and shall be accompanied by a fee of fifty thousand rupees.

Provided that where the application is for permission to import a new drug (bulk drug substance) and grant of approval to manufacture its formulation/s, the fee to accompany such application shall be fifty thousand rupees only.

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, is made, the fee to accompany such subsequent application shall be fifteen thousand rupees:

Provided further also that any application received after one year of the grant of approval for the manufacture for sale of the new drug, shall be accompanied by a fee of fifteen thousand rupees an such information and data as required by Appendix I or Appendix IA of Schedule Y, as the case may be.]

(2) The manufacturer of a new drug under sub-rule (1) when applying for approval to the licensing authority mentioned in the said sub-rule, shall submit data as given in Appendix I to Schedule Y including the results of clinical trails carried out in the country in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in the format given in Appendix II to the said Schedule.

[(2A) The Licensing Authority as defined in clause (b) of rule 21 after being satisfied that the drug if approved to be manufacture as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in the country, shall issue approval in Form 46 and/or Form 46A, as the case may be, subject to the conditions stated therein:

Provided that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission could be considered.]

> (3) When applying for approval to manufacture of a new drug under sub-rule (1) or its preparations to the State licensing authority, an applicant shall produce along with his application, evidence that the drug for the manufacture of which application is made has already been approved 3[in the name of the applicant] by the licensing authority mentioned in rule 21:
>
> Provided that the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the 4[Licensing Authority in Rule 21] may, in public interest decide to grant such permission on the basis of data available from other countries:
>
> Provided further that the submission of requirements relating to Animal Toxicology, Reproduction studies, Teratogenic studies, Perinatal studies, Mutagenicity and Carcino-genicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules."

43. Admittedly, in terms of the Rules, respondent no.2 was required to make an application as set out in Form 44, to the Licensing Authority and to also submit the data as provided in Schedule "Y" to the said Rules.

44. The proviso to Rule 122B(3) of the Rules expressly provides for waiver of the requirement of submitting results of local clinical trials in certain cases where the requisite data is available from other countries. Such requirement can also be modified or relaxed in case of new drugs approved and marketed for several years in other countries.

45. Clause (1) of Schedule 'Y' provides that an application for permission to import or manufacture new drugs is required to be made in Form-44 and is required to be accompanied by the following: (i) chemical and pharmaceutical information as prescribed in Item 2 of Appendix I; (ii) animal pharmacology data as prescribed in Item 3 of Appendix I and Appendix IV; (iii) animal toxicology data as prescribed in Item 4 of Appendix I and Appendix III; (iv) human Clinical Pharmacology Data as prescribed in Items 5, 6 and 7 of Appendix I as specified therein; (v) regulatory status of the drugs in other countries as prescribed in 9.2 of Appendix I; (vi) full prescribing information for marketing as prescribed in Item 10 of Appendix I; and (vii) complete testing protocol(s) for quality control testing together a complete impurity profile and release specifications for the product as prescribed in Item 11 of Appendix I.

46. Clause 1(3) of Schedule 'Y' of the Rules also empowers the Licensing Authority to abbreviate, defer or omit the toxicological and clinical data requirements in cases of life threatening/serious diseases or diseases of special relevance to the Indian health scenario. Clause 1(3) of Schedule 'Y' of the Rules, is set out below:-

> "(3) For drugs indicated in life threatening / serious diseases or diseases of special relevance to the Indian health scenario, the toxicological and clinical data requirements may be abbreviated, deferred or omitted, as deemed appropriate by the Licensing Authority."

47. It is indisputable that AIS is a life threatening and serious condition. Thus, plainly, the Licensing Authority is empowered to relax

toxicological and clinical data requirements as specified in Schedule 'Y' of the Rules.

48. Clause (6) of Article 2 of Schedule 'Y' of the Rules contains provisions regarding Phase I of the Clinical Trials. Sub-clause (i) of Clause (7) of Article 2 of Schedule 'Y' of the Rules clearly specifies that "*The objective of studies in this phase is the estimation of safety and tolerability with the initial administration of an investigational new drug into human(s)*". It is further specified that "*Studies in Phase I development usually have non-therapeutic objectives and may be conducted in healthy volunteers subjects or certain types of patients*".

49. The studies conducted in Phase I are intended to involve one or more combination of the objectives relating to maximum tolerated dose with pharmacokinetics/pharmacodynamics and early measurement of drug activity.

50. Provisions for Phase II of the Clinical Trials are contained in Clause (6) of Article 2 of Schedule 'Y' of the Rules. Sub-Clause (i) of Clause (7) expressly provides that the Primary objective of Phase II trials is to evaluate the effectiveness of a drug for a particular indication. One of the important objectives of Phase II of Clinical Trials is to determine the dose(s) and regimen for Phase III trials.

51. Clause (8) of Article 2 of Schedule 'Y' of the Rules contains provisions on Phase III of the clinical trials. It expressly states that "*Phase III studies have primary objective of demonstration or confirmation of therapeutic benefit(s)*". Studies in Phase III are

designed to confirm the preliminary evidence accumulated in Phase II that the drug is safe and effective for the use in the intended indication and recipient population.

52. Clause (9) of Article 2 of Schedule Y of the Rules expressly provides that these trials may not be considered necessary at the time of new drug approval but may be required by the Licensing Authority for optimizing the drug's use.

53. It is apparent from the above that Phase II and Phase III of the clinical trials need not been considered as wholly distinct. It is clear that the objective of Phase II of the trials is to evaluate the effectiveness of the drug for a particular indication. The heading of Clause (7) of Article 2 of Schedule Y of the Rules indicates that Phase II entails "*Therapeutic Exploratory Trials*". Phase III trials are conducted with the objective of demonstration or confirmation of therapeutic benefit(s). Such studies are to confirm the evidence as accumulated in Phase II. Thus, the therapeutic value of the drug as indicated during Phase II is confirmed by Phase III trials. Clearly, the clinical data collected during Phase II would also of considerable value for Phase III studies.

54. The question whether the necessary clinical trials have been conducted must be viewed bearing the aforesaid view in mind. In the present case, respondent no.2 (M/s Gennova Biopharmaceuticals Limited) had applied to DCGI by a letter dated 03.12.2008, seeking permission to conduct clinical trials with Elaxim-20 (Tenecteplase – TNK-t-PA) to assess the efficacy and safety of Tenecteplase in AIS.

The copy of the letter produced on record indicates that the clinical trial protocol along with the consent letters from investigators were enclosed therewith. It was contended on behalf of the petitioner that since 'Elaxim' was approved as being a biosimilar drug and therefore, the Similar Biologics Guidelines were required to be complied with. This contention is not persuasive. Once a drug has been approved either as being a similar biosimilar or otherwise, the said drug would stand approved for all intents and purposes including for the purposes of Rule 122 E(b) of the Rules. Thus, if the said approved drug is modified or intended to be used for a new claim, Rule 122E(b) of the Rules is required to be followed and there is no requirement for any further compliance with Similar Biologics Guidelines.

55. The NOC for holding clinical trials, as sought for by respondent no. 2, was granted by the DCGI. Although the petitioner disputes the same, however, the dispute raised in this regard is without merit, since the same is clearly evident from the letter dated 27.02.2009. The said letter was placed on record in the Writ Petition bearing number ***W.P. (C) 7357/2016 captioned Dr Deep Das v. Union of India and Another***. The said matter was initially heard along with the present petition and this letter is also included in the compilation of documents filed on behalf of respondent no. 2. The opening paragraph of the said letter expressly states as under:-

> "This Directorate has no objection to your conducting clinical trials with the said drug under the supervision of the investigators mentioned in your letter and as per the protocol Protocol No: GBL/TNK-

TPA/AIS/002 version no.02 dated 17/02/2007 forwarded to this Directorate."

56. It is affirmed on behalf of the DCGI that pursuant to the aforesaid NOC dated 27.02.2009, respondent no. 2 conducted its clinical trials and such trials was carried out on fifty patients. It is stated that twenty patients were administered doses of 0.1mg and thirty patients had been administered dose of 0.2mg. A copy of the report of October, 2010 in this regard was filed by the DCGI in a sealed cover.

57. The clinical trial report was examined by an Expert Committee on 15.06.2011. The Expert Committee noted that clinical trials in fifty patients were conducted at seventeen centers. Twenty-five patients received 0.1mg/per kg and twenty-five received 0.2mg/per kg.

58. The Committee considered the two options for evaluation. The Committee noted that the trial data provided was not consistent with Schedule 'Y' of the Rules which suggested a general figure of hundred subjects for Phase III clinical trials. The Committee thereafter evaluated the options available. It noted that the first option is to ensure that complete safety and efficacy studies in a proper sample size are conducted. This would require a large number of subjects and would be extremely difficult considering the intricacies of a trial in a case of a stroke and the limited window of intervention of three hours from the stroke. The Expert Committee also considered the other option which is to direct the manufacturer to provide data on one hundred subjects. The relevant extracts of the minutes of the meeting including the recommendation of the Committee are reproduced below:-

"3. After detailed discussions and hearing the presentations from the manufacturer and also the points put forward by the regulator, the following two options emerge:

i) **Analytical Mode I (Ideal)**

The molecule is considered as a new drug, and a complete safety and efficacy study in appropriate sample size needs to be conducted. It is noted that doing such efficacy study will require large number of subjects and an appropriate blinded comparator arm in the trial. This is very difficult considering the intricacies of such a trial in stroke including the very small window period of 3 hours from stroke to intervention.

The arguments against this approach are:

(a) This may not be so important since the mechanism of action of the TNK-t-PA and alteplase is similar and substitution of amino acids is expected to be beneficial based on published data.

(b) Such a study will take a long time and will amount to denying the relatively cheaper and possibly better or at least equally effective treatment modality to the Indian population which is presently dependent on very expensive thrombolytic drug currently available.

ii) **Analytical model II**:

This model is based on the following considerations:

1. There is similarity in the mechanism of action of TNK-t-PA with that of alteplase.

2. Use of tenecteplase in myocardial infarction is established. The data of 6000 patients has been published.

3. Clinical trials conducted outside India suggest efficacy of tenecteplase in acute ischemic stroke in trials.

4. Indian regulator had permitted the manufacturer to conduct a clinical trial of tenecteplase in 50 stroke patients which has

been completed and data submitted. This trial has been conducted by the company in 50 stroke patients at 17 centres. In this analytical framework, to fulfil the Schedule Y requirement of a phase III trial, data in 100 subjects is required.

Committee Recommendations

The committee considered analytical model II as reasonable and consistent with DCGI's original decision. But the manufacturers need to provide data on 100 subjects to be consistent with Schedule Y. This approach will, on one hand, reasonably ensure efficacy and safety of TNK-t-PA in Indian stroke patients and also reduce the time to reach the market for TNK-t-PA. This is expected to benefit the patients who cannot afford the more expensive thrombolytic therapy and succumb to stroke. However to further safeguard the interest of the Indian population, the manufacturer must be asked to carry out a PMS study and submit a detailed PSUR for TNK-t-PA in Indian population. The Committee noted that Model I is scientifically the ideal course, but has practical difficulties in implementation and there is reasonable assurance for published data that the direction of effect of the change is favourable.

The regulatory authorities may adopt one of the two approaches above, keeping in view the current regulatory policies and practices to ensure consistency in approach and scientific validity among similar proposals."

59. The aforesaid recommendations of the Committee were accepted and by a letter dated 19.08.2011, DCGI directed respondent no.2 to submit clinical data of fifty additional subject of strokes for further action.

60. Thereafter, on 17.10.2011, respondent no.2 submitted the clinical trial protocol for conducting clinical trials on fifty additional subjects of

stroke patients. DCGI by a letter dated 05.12.2013, granted the said permission to conduct trials under the supervision of two investigators named in the said letter namely, Dr Vikram Sharma and Dr Thomas Mathew. The DCGI also directed that study centers of reputed institutes having an active stroke programme be also included as study centers. DCGI also directed respondent no.2 to include study centers of reputed Government institutes having active stroke programme with dedicated staff in the Neurology department preferably at AIIMS, JIPMER, NIMHANS and the necessary information be submitted to DCGI before initiation of the studies.

61. In compliance with the aforesaid directions, respondent no.2 submitted details of seven study centers, which included the Department of Neurology, JIPMER.

62. On 22.10.2014, DCGI sent another letter amending its earlier letter dated 05.12.2013 to include additional investigatory sites. In terms of the said letter, seven additional clinical sites were included and the names of the respective investigators were also specifically mentioned.

63. It is affirmed on behalf of the DCGI that respondent no.2 submitted its clinical trial report on 13.07.2016, after conducting trials on fifty-four additional patients in terms of the permission granted earlier. The results of the clinical trial were placed before 22nd SEC (Neurology & Psychiatry) Expert Committee on 18.07.2016. After considering the said report, the Committee recommended that

marketing authorization for the drug in question be granted. It also recommended that respondent no. 2 conduct active post marketing surveillances for safety evaluation in one thousand patients. It also desired that after completion of surveillance of the first five hundred patients, the data generated be submitted to DCGI for further evaluation by the Committee. Thereafter, on 28.07.2016 DCGI granted the approval, which is impugned in the present petition.

64. It is clear from the above that DCGI had considered the extent of clinical trials required. The Expert Committee, as constituted, also examined the said requirement and made its recommendations. Clearly, the requirements of Schedule 'Y' to the Rules have not been strictly followed. This was also noticed by the Expert Committee which had evaluated various options on 15.06.2011. However, the Expert Committee accepted that it would be reasonable not to adhere to the ideal course in view of the practical difficulties in implementation and on account of a reasonable assurance by virtue of publicized data. DCGI did not find any necessity for Phase I studies as the same were only required for purposes of safety and tolerability. As noticed hereinbefore, Sub-Clause (i) of Clause (6) of Article 2 of Schedule 'Y' to the Rules expressly provides that Phase I trials could be conducted in healthy volunteers. This is so, because the objective is only to estimate safety and tolerability of the drug in question. In the present case, the drug in question, in a higher dose, had been approved for AMI. Thus, it is apparent that the evaluation of safety and tolerability in humans was not required to be conducted.

65. Insofar as Phase II and Phase III trials are concerned, DCGI had examined the requirement and had permitted the trials to be conducted as per the clinical trial study protocol submitted by respondent no.2. The said protocol was for conducting Phase II/Phase III trials on a sample size of fifty patients. It is not necessary in all cases that the work done and data generated in the two phases be treated as mutually exclusive.

66. On the directions of the DCGI, respondent no.2 had conducted trials on fifty-four additional patients (even though the DCGI had directed that the trials be conducted on fifty additional patients). As noticed hereinbefore, there is certain amount of overlap between Phase II and Phase III trials and it is not necessary that Phase II trials be excluded for the purposes of Phase III trials.

67. The DCGI had also filed several documents wherein permission had been granted to various other manufacturers for jointly conducting different phases of trials.

68. This Court is of the view that the subject of clinical trials cannot be viewed in a straight-jacket formula and it would be open for DCGI to mould the extent of clinical trials keeping in view the objectives sought to be achieved. It is clear in the present case that Phase I of clinical trials was not required and the DCGI has specified that the objectives of Phase II and Phase III have been served by the clinical trials conducted by respondent no.2.

69. The extent of clinical trials required and whether the same can be abbreviated is a matter to be considered by experts and the concerned

authority. No interference with the decision on merits is warranted in proceedings under Article 226 of the Constitution of India, unless it is established that the same is *malafide*, capricious or fails the Wednesbury test, that is, no sensible person could possibly arrive at the said decision.

70. This Court is unable to accept that in the present case the said threshold for interference under Article 226 of the Constitution has been met. On the contrary, this Court finds no infirmity in the manner in which the DCGI has proceeded. The petition is unmerited and is dismissed with costs quantified at ₹50,000/- to be payable to each of the respondents. The said costs will be paid within a period of two weeks from today.

71. All pending applications are also disposed of.

VIBHU BAKHRU, J

OCTOBER 21, 2019
MK/pkv