IN THE HIGH COURT OF DELHI AT NEW DELHI

% Judgment delivered on: 05.07.2019

\+ **W.P.(C) 7073/2018 and CM Nos. 26897/2018 &47277/2018**

M/S THEMIS MEDICARE LIMITED ..... Petitioner

Versus

UNION OF INDIA AND ORS. ..... Respondents

Advocates who appeared in this case:

For the Petitioner :Mr C. S. Vaidyanathan, Senior Advocate with Ms Gunita Pahwa, Mr Raj Dutt and Mr Prashant Dagar, Advocates.

For the Respondents :Mr Kirtiman Singh, CGSC with Mr Prateek Dhanda, Ms Shruti Dutt and Mr Waize Ali Noor, Advocates for R-1 to R-5.
Mr Rahul Verma, Addl. Advocate General for State of Uttarakhand/R-7.
Mr Abhinav Vasisht, Sr. Advocate with Mr Manish Aggarwal, Mr Anuj Malhotra and Mr Raghav Pandey, Advocates for R-8.
Mr Shadman Ali, Advocate for U/Tribunal Daman and Diu.

AND

\+ **W.P.(C) 8672/2018& CM No. 33293/2018**

M/S GATTEFOSSE SAS AND ANR. ..... Petitioners

Versus

UNION OF INDIA AND ORS. ..... Respondents

Advocates who appeared in this case:

For the Petitioner : Mr Rajeev Bansal, Sr. Advocate with Ms

Gunita Pahwa, Mr Raj Dutt Singh, Mr Prashant and Ms Parul Panthi, Advocates.

For the Respondents :Mr Kirtiman Singh, CGSC with Mr Prateek Dhanda, Ms Shruti Dutt and Mr Waize Ali Noor, Advocates for R-1 to R-5.
Mr Rahul Verma, Addl. Advocate General for State of Uttarakhand/R-7.
Mr Abhinav Vasisht, Sr. Advocate with Mr Manish Aggarwal, Mr Anuj Malhotra and Mr Raghav Pandey, Advocates for R-8.
Mr Shadman Ali, Advocate for U/Tribunal Daman and Diu.

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HON'BLE MR JUSTICE VIBHU BAKHRU

JUDGMENT

VIBHU BAKHRU, J

1. The petitioners have filed the present petition, *inter alia*, impugning the recommendations of an Expert Committee (as communicated by a letter dated 27.12.2017) constituted by Government of India under the chairmanship of Dr. Girish Sahani, Director General CSIR (hereafter referred to as 'the Third Committee') to, *inter alia*, examine and assess whether Transcutol P can be permitted for human use in parenteral formulations. The petitioners also impugn the communications dated 04.07.2018 and 09.07.2018 sent by respondent no. 5 (Drugs Controller General of India – DCGI) to Drug Licensing Authorities of the State of Uttarakhand and the Union territory of Daman and Diu to cancel the petitioner's licenses to manufacture Diclofenac Sodium Injection 75 mg/ml containing Transcutol P (hereafter "the drug in question"). The said communications were sent

by DCGI on the basis of the letter dated 27.12.2017, issued by the Chairman of the Third Expert Committee and minutes of the meeting dated 20.12.2017 of the Third Expert Committee.

2. The petitioner in W.P. 7073 of 2018 (M/s Themis Medicare Limited – hereafter "the petitioner") is a pharmaceutical company which manufactures the drug in question – Diclofenac Sodium 75 mg/ml Injection – containing Transcutol P as an excipient under various brand names. Diclofenac Sodium injection 75 mg/ml is marketed by M/s Novartis India Limited (hereafter "Novartis") under the brand name "Voveran 1ml". The petitioner's patent for its injection is pending in India.

3. The petitioner in W.P. 8672 of 2018 (M/s Gattefosse, France – hereafter "Gattefosse") manufactures the Transcutol P used by the petitioner. Gattefosse is the sole manufacturer and supplier of Transcutol P for parenteral purposes.

4. The Third Committee had recommended that Transcutol P as an excipient in parenteral formulations, needs to be tested for its toxicity independently in order to establish its safety as it found no evidence that the same could be used in parenteral formulations. The petitioners dispute the same and contend that there is sufficient material to establish that use of Transcutol P in parenteral form is safe. This is the principal controversy involved in these petitions.

Factual Background

5. Respondent no. 8 (M/s Troikaa Pharaceutical Ltd. – hereafter "Troikaa") applied to DGCI for approval of the drug in question containing Glycurol as an excipient as a "new drug" under Rule 122E of the Drugs and Cosmetic Rules (hereafter 'the Rules'). On 30.07.2007, DCGA approved the drug in question as a new drug under Rule 122E of the Rules. On the basis of the said approval, on 17.08.2013, the petitioner applied for and was also granted License to manufacture the drug in question by the Drugs Licensing Authority, Daman and Diu. The petitioner was, thereafter, granted license to manufacture the drug in question by the Drugs Licensing and Controlling Authority, Uttarakhand on 04.04.2016.

6. In June 2013, the petitioner started manufacturing the drug in question. Pursuant to this, the petitioner also entered into an agreement with Novartis for selling the aforesaid formulation under the brand name 'Voveran 1 ml'.

7. The petitioner claims that the petitioner and Novartis gained the leadership position in the market which led to the decline of the market share of one of the competitors, Troikaa. The petitioner further claims that due to the decline in market share, Troikaa manipulated and misled various State and Central Agencies against the petitioner regarding use of Transcutol in parenteral preparations.

8. In November, 2015, DCGI received complaints from doctors against the petitioner's formulation. The petitioner claims that the

above-mentioned complaints were motivated and at the instance of Troikaa.

9. The petitioner received a letter dated 04.09.2015 from the Joint Drug Controller, CDSCO (DCGI), asking the petitioner to submit a clarification regarding the use of Transcutol in the Diclofenac Sodium Injection and the details of the excipients used in the formulation of the Diclofenac Sodium injection.

10. The petitioner claims that on 22.09.2015 it submitted eleven studies – studies on Transcutol, repeated dose toxicity studies and single dose studies – in response to the letter received from DCGI. On 09.11.2015, the petitioner submitted additional data to DCGI with reference to the same.

11. The petitioner received a communication dated 10.12.2015 from the SND Division of DCGI to attend a meeting scheduled on 18.12.2015 of an Expert Committee formed by DCGI (hereafter "First Expert Committee") to review the safety and permissibility of "Diethylene Glycol Monoethyl Ether" (DEGEE). It is relevant to note that Transcutol P is a refined version of the said compound, DEGEE.

12. The representative of the petitioner appeared before the First Expert Committee and made its presentation on 18.12.2015. The First Expert Committee opined that an expert group would review the pre-clinical toxicity study data generated by the petitioner at Sipra Labs Ltd. Thereafter, on 27.01.2016, DCGI formed an expert group to conduct inspection at Sipra Labs Ltd.

13. Thereafter, the inspection (for the verification of toxicity data submitted by the petitioner) was conducted on the scheduled date of 01.02.2016.

14. On 03.02.2016, the petitioner sent a letter to DGCI, which was followed by an e-mail on 8.02.2016 regarding its comments on the meeting held at Sipra Labs Ltd.

15. On 17.02.2016, DCGI sent a communication calling upon the petitioner to attend the second meeting of the First Expert Committee on 19.02.2016. The petitioner made a representation before the First Expert Committee on 19.02.2016. The petitioner claims that it also forwarded the clarifications on the points discussed in the second meeting of the First Expert Committee to the Joint Drugs Controller. The petitioner also sent a letter to the Joint Drugs Controller regarding the permission granted by CDSCO in the year 2007 on the Tolperisone Injection, which contained Transcutol.

16. The petitioner claims that on 22.02.2016, it submitted further studies pursuant to the second meeting of the First Expert Committee, namely, five studies and four placebo studies. Thereafter, on 25.02.2016, the petitioner sent an email to the Assistant Drug Controller, Delhi, submitting additional information on PSUR data and safety data. The petitioner claims that it also submitted six compact discs to DCGI containing safety data of Diclofenac Sodium Injection.

17. The petitioner claims that there was a third meeting of the First Expert Committee held on 29.03.2016, but the petitioner was not invited to the said meeting.

18. On 31.03.2016, the petitioner sent a letter to the Joint Drugs Controller informing him about the sale of Tolperisone Injection with Transcutol in CIS Countries for human usage.

19. In March, 2016, the First Expert Committee submitted its report, *inter alia*, stating that "*the data/information submitted by M/s. Themis Medicare Ltd. and that available in the public domain regarding use of Diethylene Glycol Monoethyl Ether (DEGEE) in parenteral formulations has been thoroughly reviewed and examined by the committee constituted for this purpose. In view of the above, the committee opined that available scientific evidence is not adequate to demonstrate safety/tolerability of DEGEE (Transcutol-P) in parenteral preparation for human use".*

20. The petitioner claims that the above mentioned recommendation was not communicated to the petitioner and the petitioner came to know that DCGI, vide its letter dated 13.04.2016, had informed the Drug Licensing Authority of Daman and Diu and the Licensing Authority, Uttarakhand that DCGI had reached the conclusion that the use of Transcutol on parenteral preparation for human use is not safe. DCGI also requested the State Licensing authorities to immediately cancel the license, sale and distribution of Diclofenac Sodium Injection, till the

petitioner submits safety, tolerability data to CDSCO for review and further action.

21. Aggrieved by the aforesaid, the petitioner made a representation on 21.04.2016 before DCGI seeking an appointment for personal hearing and the copies of the minutes of all meetings of the First Expert Committee.

22. On 26.04.2016, the petitioner gave its representation to DCGI. On the same day, Gattefosse issued a letter to the petitioner informing that no product was withdrawn due to the use of Transcutol as an excipient.

23. On 30.04.2016, the petitioner sent another letter to DCGI in response to the issues discussed in the meeting held on 26.04.2016. In view of the petitioner's representation, respondent no. 1 decided to form another committee to examine the matter.

24. Accordingly, DCGI vide its letter dated 05.05.2016 informing the Drugs Controlling and Licensing Authority, Uttarakhand and Drugs Controlling and Licensing Authority, Daman and Diu, that another expert committee would be formed to examine the issue and action was to be taken subject to the report of the expert Committee.

25. On 10.05.2016, the petitioner received another letter from the CDSCO (SND Division) dated 04.05.2016, regarding the finding of the First Expert Committee on the safety and the tolerability of Diclofenac Sodium Injection containing Transcutol. The petitioner made a

representation dated 16.05.2016 disputing the aforesaid findings of the First Committee Expert Committee.

26. Thereafter, DCGI constituted another expert committee (hereafter "Second Expert Committee") to re-examine the safety and tolerability of DEGEE for its use in the drug in question.

27. On 07.06.2016, DCGI sent another letter, *inter alia*, intimating the petitioner that first meeting of the expert committee would be held on 10.06.2016.

28. In the meantime, Troikaa filed a writ petition before this court (W.P.(C) 4715/2016), *inter alia,* praying for prohibiting the manufacture, sale, and/or distribution of the drug in question (Diclofenac Sodium Injection 75 mg/ml) containing Transcutol and prohibiting the manufacture, sale or distribution of any parenteral preparation/s containing Transcutol. By an order dated 26.05.2016, this Court directed all the parties to avail the opportunity of hearing before the Second Expert Committee.

29. The first meeting of the Second Expert Committee was held on 10.06.2016, wherein the representatives of the petitioner and Troikaa made their representations. The Second Expert Committee submitted its report dated 25.07.2016, wherein it concluded that the use of Diclofenac injection having Transcutol P does not have any safety concerns, which warrants its suspension.

30. DCGI, in its counter affidavit filed W.P.(C) 4715/2016, submitted that the report of the Second Expert Committee will be examined by the CDSCO for further action in terms of the recommendations made in the report of the Second Expert Committee. However, the petitioner submits herein that the respondent did not act on the recommendations made in the report of the Second Expert Committee.

31. The Joint Secretary of Health and Family Welfare, also issued a note dated 11.03.2017 regarding the controversy in relation to the petitioner's formulation of the drug in question. It was concluded that: (i) the recommendations of the Second Expert Committee appeared to be quite stringent and would be able to capture any adverse events; and (ii) the present case appeared to be a business rivalry aimed at protecting commercial interest more than a case of scientific issues. In the aforesaid view, it was recommended that the issue should be closed and CDSCO should take further action as per the recommendations of the Second Expert Committee.

32. The Central Government, by an order dated 03.05.2017, constituted a Review Committee on the same issue (hereafter "Third Expert Committee"). By a communication dated 05.07.2017, the petitioner was called upon to attend the second meeting of the Third Expert Committee scheduled to be held on 12.07.2017.

33. Thereafter, the petitioner made another representation on 12.07.2017 before the Third Expert Committee. It is submitted that

pursuant to the second meeting of the Third Expert Committee, the petitioner submitted a main file, along with 11 other technical back-up data files to the Chairman of the Third Expert Committee consisting of all relevant documents on 21 July 2017.

34. The petitioner claims that three meeting of Third Expert Committee were held (dated 14.06.2017, 12.07.2017, and 20.12.2017), out of which the petitioner attended only one meeting. The petitioner claims that it has not been provided a copy of any minutes of any of the said meetings.

35. The Deputy Secretary of the Ministry of Wealth and Family Welfare, by a letter dated 23.10.2017, called upon the petitioner for early submissions of its recommendations on safety and tolerability of DEGEE (Transcutol P) in Diclofenac Sodium Injection.

36. In the meantime, the Indian Pharmacopoeia Commission (hereafter 'IP Commission') issued the draft of the Eighth Edition of the Indian Pharmacopoeia for public comments. In the said draft, the monograph on Diethylene Glycol Monoethyl Ether was included. However, the monograph on DEGEE under labelling requirements stated that DEGEE cannot be used for parenteral preparations.

37. Thereafter, the petitioner made its submissions on 04.12.2017 to IP Commission regarding the amendment of monograph on DEGEE (for deletion of the statement that it is not to be used for parenterals). Further, Novartis also made its submissions to the IP Commission for amendment of the DEGEE monograph vide its email dated 13

December, 2017. Thereafter, the petitioner further provided the additional information as sought by the representatives of the IP Commission.

38. The Third Expert Committee, in its third meeting held on 20.12.2017, made recommendations that the issue whether Transcutol P could be used, especially in parenteral form, was to be determined by the Drug Regulatory Authority.

39. Thereafter, The IP Commission amended IP, 2018 and deleted the labelling requirement for DEGEE. The petitioner was informed of the said amendment vide the letter dated 03.01.2018.

Submissions

40. Mr Vaidyanathan, learned senior counsel appearing for the petitioner contended that the findings of the Third Committee are perverse, illegal, arbitrary and devoid of any reasons. It is also contended on behalf of the petitioner that the decision of the respondent authorities to constitute the Third Expert Committee was also arbitrary and unreasonable.

41. He contended that the decision making process of the Third Committee is flawed for the reason that (i) no report or document deliberated upon by the Third Committee was mentioned in the minutes; (ii) its view was not substantiated by any other material; (iii) the Third Committee did not address the terms of reference; (iv) that the safety data furnished by the petitioner and the cover of its letter dated

21.07.2017 was not deliberated; (v) Gattefosse being the sole manufacture of Transcutol P, was not invited to make its submissions before the Third Committee even though it had been resolved by the Third Committee that Gattefosse would be invited to make its submissions; (vi) that the Third Committee acted in a hasty manner and returned its findings without considering the petitioner's request not to consider the DEGEE monograph as appearing in Indian Pharmacopoeia, 2018 which was subsequently deleted; (vii) that the quorum of the Third Committee was not complete as three members including Toxicologist, were not present at the final meeting.

42. In addition to the above, the petitioner also contested the view of the Third Expert Committee on merits.

43. It was contended on behalf of the petitioner that there are no safety issues with regard to use of Transcutol P in a parenteral form and the same has been approved by CDSCO in 2010 in another formulation. It was stated that CDSCO had approved Tolperisone Injection in 2010 and the said formulation contained Transcutol P as an excipient. The petitioner contended that the Third Committee had failed to consider that clinical trials for Tolperisone Injection containing Transcutol P were conducted and its safety for human use was established.

44. Mr Vaidyanathan also relied on the report of the Second Committee and contended that the Second Committee had, after examination of all safety data, accepted that Transcutol P did not have

any safety concern. In addition to the above, the petitioner also countered the submissions made on behalf of Troikaa.

45. Mr Bansal, learned senior counsel appearing for Gattefosse reiterated the contentions as advanced on behalf of the petitioner regarding safety of Transcutol P. It was further contended that Indian Pharmacopoeia Commission (IP Commission) has initiated a nationwide Pharmacovigilance program and it had not found any safety concern with the excipient Transcutol P. He submitted that there were no adverse events reported in respect of use of Transcutol P as an excipient. He also earnestly contended that principles of natural justice were violated as Gattefosse was not invited to make any presentation by the Committee with regard to toxicity data generated on Transcutol P. He submitted that the decision of the respondents amounts to placing a complete ban on the use of Transcutol P, which is highly prejudicial to the interest of Gattefosse and yet Gattefosse was provided no opportunity to address the concerns regarding the use of Transcutol P.

46. Mr Abhinav Vashisht, learned counsel appearing for Troikaa contended that Troikaa was granted the permission to manufacture the drug in question (Diclofenac Sodium 75 mg/ml Injection) with the excipient Glycofurol (Dynapar AQ) as a new drug under Rule 122B and 122E of the Rules after it had conducted all necessary tests and clinical trials. He submitted that the petitioner had obtained the license for manufacturing the drug in question on the basis of the permission granted to Troikaa in respect of its drugs Dynapar AQ. He submitted that the drug manufactured by the petitioner was not identical inasmuch

as it used the excipient Transcutol P, which was different from the excipient contained in Dynapar AQ; nonetheless, the petitioner had not furnished any safety data or conducted any clinical trials in obtaining approval of its drug. Next, he submitted that the DEGEE is not permitted as an excipient in any of the developed countries including USA, Europe, Australia, Canada and various other countries.

Reasons and Conclusion

47. At the outset, it is necessary to observe that the scope of judicial review of the decision of the respondent authorities is limited. Its decision can be interfered with only if it found that there is serious flaw in the decision-making process or that the decision is so perverse and unreasonable that it fails the *wednesbury test;* that is, no sensible person could possibly arrive at the said decision.

48. The decision of the respondent authorities and the Third Committee is required to be tested bearing the aforesaid in mind.

49. It was contended on behalf of the petitioner that Troikaa had manipulated and misled various drug agencies regarding the use of Transcutol P in parenteral formulations. It was submitted that this was a case of business rivalry and the decision of the respondents to form a Committee was unwarranted. It was also contended that more than thirteen crore ampoules of the drug in question had been sold and there is no report of any serious adverse event. Therefore, there could be no issue regarding the safety of the Transcutol P as an excipient.

50. Indisputably, the respondent authorities had received various communications from Troikaa raising the safety concerns regarding use of Transcutol P as an excipient. It was alleged that use of Transcutol P was unsafe due to nephrotoxicity of the said excipient.

51. In view of the above, the decision of the respondent authorities to constitute an Expert Committee to examine the matter regarding safety of Transcutol P in injectable formulations can by no stretch be said to be arbitrary, unreasonable or unwarranted. Plainly, the respondent authorities would be failing in their duty if they failed to examine an issue relating to safety of the drugs once it was brought to their notice.

52. The First Committee was constituted by an order dated 09.12.2015. The said Committee submitted its recommendations on 18.03.2016. The petitioner claimed (as it has done in this case) that the use of the Transcutol P as an excipient was approved by DCGI. This was founded on the basis that in the year 2010, DCGI had granted approval for manufacture of the drug Tolperisone Injection, which in turn contained DEGEE as an excipient. This contention was rejected by the First Committee for the reason that approval of a product does not necessarily entail approval of the excipients used. The First Committee also noted that Tolperisone Injection was not marketed in the country and it had been withdrawn from European Market. The petitioner does not dispute that the said drug (Tolperisone Injection) has not been marketed in the country and also been withdrawn from the European Market; however, it contends that the same is not on account

of the excipient contained in the said drug and, therefore, DEGEE (or Transcutol P) should be construed as approved by the Licencing Authority. In this regard, the First Committee observed that the petitioner has not produced any evidence in support of its justification that Trombavar and Tolperisone Injection, containing DEGEE as an excipient was withdrawn from UAE market for reasons other than the safety concerns of the DEGEE.

53. It is not necessary for this Court to examine in detail the reasons for withdrawal of Tolperisone from EU market or for the said drug not being marketed in India. However, suffice it to state that currently no drug is being marketed in India other than Voveran, which uses DEGEE (or Transcutol P) as an excipient. In addition to the above, the First Committee also noted that the French Agency for Safety of Health Product (AFSSAPS) had suspended the marketing authorisation for SIPHON buvable© solution (Prthosiphon) and PILOSORYL© containing Transcutol (DEGEE) due to certain adverse events. The petitioner does not dispute that the said medicines were withdrawn by AFSSAPS. However, it contends that the said drugs were withdrawn on account of misuse of dose and other reasons. This remains a contentious issue.

54. Admittedly, USFDA has also not accepted DEGEE for parenteral use. Similarly, the concerned authorities in Australia, Canada and Europe have not approved use of any drug containing Transcutol P as an excipient in parenteral form. It is pointed out that use of DEGEE is restricted for topical use only in these countries. It was earnestly

contended on behalf of the petitioner that this was so because no company had sought for an approval of a drug containing Transcutol P as an excipient and the fact that there was no approved drug containing Transcutol P as an excipient, ought not to be construed to mean that the said countries had proscribed the use of Transcutol P as an excipient.

55. At this stage, it is relevant to refer to observations made by the First Committee to the submissions made on behalf of the petitioner. The relevant observations are set out below:-

> "I. Comments of the Committee on the reply of M/s Themis Medicare
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> i. The committee observed that DCGI has granted permission to the drug Tolperisone Injection in year 2010, vide permission No. MF-673/2010. Though approval for Tolperisone injection was granted, no separate approval or mention has been made regarding the use of DEGEE as excipient in the formulation. Approval for the drug product does not warrant the approval of the excipients. The committee observed that the firm has not submitted any documentary evidence to exonerate DEGEE in the withdrawal of Tolperisone Injection from the European market. The committee also observed that the product Tolperisone Injection manufactured by M/s Themis is not marketed in the country.
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> ii. The Firm submitted conclusion of the Mutagenicity study report of Transcutol P Bacterial reverse mutation test (plate incorporation) by Chrysalis preclinical services, Europe sponsored by M/s Gattefosse. The complete report has not been submitted except for

concluding page. No inference can be drawn out of the conclusion of the study as the raw data of this study is not available. Genotoxicity and carcinogenicity data for Transcutol P by injectable route has not been submitted.

iii. Selection of dose of Diclofenac Injection 75/ml with Transcutol P with experimental data such as LD50 and also LOAEL/NOAEL with the DEGEE (Transcutol-P) by intended route of administration (i.v/i.m)is not demonstrated.

iv. Firm has stated that Trombavar and Tolperisone Injection containing DEGEE as an excipient were withdrawn from EU market not because of safety concerns of DEGEE. It has not produced any evidence to support its justification.

v. Further committee also observed that the French agency for safety of health product (AFSSAPS) has suspended the marketing authorization SIPHON buvable© solution (Prthosiphon) and PILOSURYL© containing Transcutol (DEGEE) due to reports of serious cases of kidney and neurological damage. Further the suspension of Authorization for the marketing of pharmaceutical product mentions both the drugs contain as excipients Monoethyl Diethylene Glycol (or DEGEE marketed under the name Transcutol implicated in the occurrence of serious side effects seen with PILOSURYL (Enclosed at annexure 12).

vi. Committee reviewed both the PSUR's and noted that the there is no safety data was reported by M/s Themis Medicare and M/s Novartis has reported very few cases which are grossly inadequate considering the quantum of the doses sold.

vii. Further the committee also review the spontaneous reports generated through PVPI for Voveran injection which shows about 45 ADR being spontaneously reported since 2014 in which 2 ADRs reported renal failure and one Azotemiea. Further due to paucity of time the individual cases have not been analyzed for causality.

II. General Observation

Comments based on existing data:

i. Diclofenac is known to have potential nephro-toxicity. Further, as per reviewed published literature DEGEE has known to be nephro-toxic. Therefore using DEGEE with Diclofenac likely to have additive/synergistic adverse effect on the renal system.
ii. The French agency for safety of health product (AFSSAPS) has suspended the marketing authorization SIPHON buvable© solution (Prthosiphon) and PILOSURYL © containing Transcutol (DEGEE) due to reports of serious cases of kidney and neurological damage.
iii. USFDA data base on inactive ingredients with respect to DEGEE is not more than 15%w/w for topical preparation (emulsion and creams) approved products.
iv. USP NF33 has a monograph DEGEE (Transcutol). The monograph recommended the labeling requirements as 'Label is to indicate that it is intended for topical or transdermal use only and it is stored under an atmosphere of an inert gas. The material is not to be used for parenterals'.
v. M/s Themis Medicare has submitted a certificate from M/s Gattefosse SAS, France stating that Transcutol-P/Transcutol HP are recommended for use in the human

pharmaceutical formulation to be administered through parenteral route.

As per the information posted on M/s Gattefosse website (http://www.gattefosse.com/en/applications/transcutol-p.html). Transcutol-P is recommended for topical products only for human use. Enclosed at annexure 13.

III **Expert committee observations**

i. Both, Transcutol-P as well as Diclofenac sodium are known to have potential nephro-toxicity. The Diclofenac sodium injection containing Transcutol-P (DTP) contains DEEGEE (Transcutol-P) and Diclofenac sodium and both are known to have potential nephro-toxicity.

ii. M/s Themis Medicare has submitted a certificate from M/s Gattefosse. SAS, France recommending the use of Transcutol-P/Transcutol HP as excipients in parenteral formulations. However, the certificate did not specify any permissible safety limits of Transcutol-P for parenteral use. The USP monograph also recommends DEGEE for topical or transdermal use only and not to be used for parenterals.

iii. The reports of all toxicological studies (11 Nos) were tested at the maximum dose of 1.5X (as presented by the authorized representative of the firm during the meeting held on 18.12.2016) of the Transcutol in their marketed product by i.v/i.m route. This level of

exposure will not confirm the safety margin of the DTP.

iv. The non clinical studies (animal toxicology) did not incorporate a study group with vehicle (Transcutol-P) used in the DTP. However, the firm has submitted a single dose toxicity study report (Study no 751212) of Diclofenac sodium injection placebo in rat by intramuscular route.

v. The reports of experimental studies do not demonstrate LOAEL/NOAEL with the DEGEE (Transcutol-P) by intended route of administration (i.v/i.m).

vi. It is essential to support the safety of the DTP by toxicokinetic data along with animal pharmacology data for Transcutol-P as required under Schedule Y.

V. **Comments on Non-clinical Toxicology**

Study specific Observations

M/s Themis Medicare Ltd has submitted a comparative repeated Dose (14 days i.v route) toxicological study report (Study No. 57522) of investigational Product (IP) in comparison to marketed product (Diclofenac Sodium Injection 75mg/ml manufactured by M/s Themis vs Vovran Injection) in Wistar Rats.

i. The study has been under taken in 5 groups with three male and three females in each group. Vehicle control group with saline, low dose group with investigational Product (6.75 mg/kg once daily), low middle dose with

Investigational Product (6.75 mg/kg twice daily), middle dose with Investigational Product (10.13 mg/kg twice daily), High dose with Investigational Product (IP) (13.5 mg/kg twice daily). It is mentioned that low dose group with Investigational Product (6.75 mg/kg once daily) is considered equivalent 75mg / adult human clinical dose.

ii. The Study results demonstrated significant pre terminal death in low middle dose with investigational Product (6.75 mg/kg twice daily), middle dose with Investigational Product (10.13 mg/kg twice daily), High dose with Investigational Product (13.5 mg/kg twice daily). In addition it is also mentioned that mortality was recorded in studies on both the products.

iii. The committee observed the sponsor's explanation that the mortality is in all groups and is not related to IP.

iv. The cause of mortality is not defined and no substantial data is also made available to evaluate the safety of DEGEE."

56. Based on the aforesaid comments, the First Committee made the following recommendations: -

"**<u>Recommendations of Expert committee</u>**

The data/information submitted by M/s Themis Medicare Ltd and that available in the public domain regarding use of Diethylene Glycol Monoethyl Ether. (DEGEE) in parenteral formulations has been thoroughly reviewed and examined by the committee constituted for this

> purpose. In view of the above, the committee opined that available scientific evidence is not adequate to demonstrate safety/tolerability of DEGEE (Transcutol-P) in parenteral preparation for human use."

57. It is apparent from the above that the First Committee flagged several issues. It took note of the the data available in public domain and expressed its opinion that the scientific evidence was not adequate to demonstrate safety/tolerability of DEGEE in parenteral preparation for human use. It is important to note that the said Committee did not opine that the DEGEE/Transcutol P was unsafe and ought to be banned. It merely indicated that the data available was not sufficient to conclude to be contrary.

58. The petitioner contests the aforesaid view. However, undisputedly, the drug manufactured by the petitioner, Voveran using Transcutol P as an excipient has not been approved by DCGI. The petitioner has not gone through the process as provided under the Rules for seeking approval of the said drug as a new drug. On the contrary, it is obtained its license to manufacture on the basis that the drug manufactured by it is not a new drug. This is difficult to accept because the drug approved by DCGI, Dynapar AQ – on the basis of which the petitioner has obtained the license to manufacture the drug in question – does not contain Transcutol P as an excipient. The petitioner may be correct that none of the advanced countries such as United States, Canada, EU countries and Australia have approved any drug using DEGEE in the parenteral form as no such permissions were sought, however, this would only mean that none of the said countries have

examined the use of DEGEE as an excipient from the standpoint of safety for human use. Viewed in this context, the decision of the First Committee that available scientific evidence for demonstrating safety/tolerability of the DEGEE in parenteral preparation is inadequate, warrants no interference. It is not apposite for this Court to enter into controversy as regarding sufficiency of scientific evidence and data regarding safety of DEGEE (or Transcutol P). The views of the Expert Committee in this regard must be accepted as there are sufficient reasons indicated in the First Committee Report to justify its view.

59. The petitioner was, obviously, not satisfied with the opinion of the First Expert Committee and made several representations for setting up another Committee for assessing the tolerability of DEGEE (Transcutol P). The Government of India acceded to the said representation and another Committee was constituted under the Chairmanship of Director General Health Services (the Second Committee). The Second Committee re-examined the matter and its conclusions are set out below: -

> "D. Conclusion:
>
> 1. Committee noted that several facts have now been brought to notice of this committee which were not available to the earlier committee. After the perusal of all information available the committee is of opinion that in the dosage and the duration of use of diclofenac injection having Transcutol P does not have safety concerns which warrants its suspension.

2. Although Pharmacovigilance is still not strong in the country, the fact that of the 308 ADR reports, in none the causality was certain and in most there were multiple medications and the fact that large number of dosage have been administered do not raised safety concerns.

3. The committee is conscious of the potential of nephrotoxicity of diclofenac preparations and therefore recommends that : -

   a) All diclofenac preparations be placed under focused Pharmacovigilance programme (PVPI) for intense monitoring.

   b) Manufacturer of diclofenac injection 75 mg/ml with Transcutol-P® be asked to submit prospective active PMS data on 2000 patients covering different parts of the country and submit safety data to the regulator for further evaluation and consideration.

   c) Firm should also submit the product information brochure clearly depicting the precaution, contra-indication and maximum duration of its use."

60. Although the Second Committee concluded that Transcutol P does not have safety concerns that warrants its suspension, it also recommended that all Diclofenac preparations be placed under focused Pharmacovigilance program and the petitioner (manufacturer of Diclofenac preparation of 75mg/ml with Transcutol P) be asked to submit prospective active PMS data on 2000 patients covering different parts of the country to the Regulator for further evaluation and consideration. It also recommended that the product information

brochure to also clearly indicate the precautions, contra-indications and maximum duration of its use.

61. It appears from the above that although Second Committee had expressed that suspension of the Diclofenac Injection was not warranted on account of safety concern, it had also indicated that it had certain reservations warranting further evaluation.

62. The observations made by the Second Committee are also relevant, as the same clearly indicate that the Second Committee also had certain reservations regarding use of Transcutol P. The said observations are set out below: -

> "10. Broadly the committee made following observation
>
> a) A formulation of tolperisone hydrochloride injection 100 mg containing Transcutol-P® as excipient was considered and permitted for clinical trial and subsequently for market authorization by CDSCO on 26.08.2010 which was never introduced in the market by the firm. It was informed by the regulator that at that time no specific attention was paid to the excipient unless there was any specific concern. Manufacturing permission issued to M/s Themis annexed at-6.
>
> b) It was noted that in no other country, to the best of knowledge of the committee and the regulator any parenteral preparation having Transcutol-P® is marketed currently. However one preparation Mydeton solution for injection (1ml solution for injection contains 100 mg of toleperisone and 2.5 mg of lidocaine hydrochloride) was marketed in Hungary, which was subsequently withdrawn from the market. The reason for withdrawal was non

efficacy of the active ingredient tolperisone. That there was any safety concern for withdrawal, could not be traced. (EMA: Question and answers on the review of tlperisone containing medicines Annexure-7)

c) Regarding the toxicity of DEGEE it was noted that the earlier reported toxicities, importantly nephrotoxicity was because of the high concentration of impurities, mainly ethylene glycol (EG) and diethylene glycol (DEG), reference (i) 'Fellows Jk, Luduena Fp, Hanzlik Pj. Glucuronic acid after diethylene glycol monoethyl ether (carbitol) and some other glycols. J PharmacolExpTher. 1947 Mar; 89(3);210-3, Annexed at 8.

d) The currently used DEGEE is much purer (99.8%) which obviates the nephrotoxic potential. Certificate of analysis and Technical data sheet of Transcutol-P® is Annexed at-9.

e) The committee also perused that literature wherein few herbal oral formulations (Urosiphon and Pilosuryl) containing Transcutol as excipient were withdrawn by European countries. Suspension authorization for the marketing pharmaceutical speciality UROSIPHON is annexed at-10.

f) Pharmacokinetic studies of DEGEE reported in the literature reveals that is excreted (about 68%) in the form of Ethoxyethoxy acetic acid within 12 hrs after administration (reference review article metabolism and disposition of glycol ether Drug Metabolism review 18(1) 1-22 (1987) annexed at 11). Another article "A review of the nonclinical safety of Transcuto a highly purified form of diethylene glycol monoethyl ether (DEGREE) used as a pharmaceutical excipient." Food and Chemical

Toxicology 72 (2014) 40-50 annexed at 12 mentions, that the pharmacokinetics for DEGEE indicates that it is well absorbed, up to 52% via the dermal route. Following absorption, DEGEE is rapidly and largely metabolized to ethoxyethoxyacetic acid (83%) with a much smaller amount (5.4%) being metabolized to diethylene glycol. The majority of the metabolites, and a small amount of the unchanged compound, are excreted in the urine within the first 34 h following exposure. What is the threshold level of exposure of this metabolite and what is the toxic potential of this metabolite is not available.

g) The impurity of DEGEE (i.e DEG and EG) gets metabolised in oxalic acid which is known to promote the formation for crystals and can be injurious to kidney. Such a possibility is negligible, since these impurities as such are less than 0.3% (as per specification of Transcutol). Certificate of analysis and Technical data sheet of Transcutol-P® is Annexed at-9.

h) The Pharmacovigilance Programme of India (PvPI) started in 2010 and is gradually increasing its capacity. The PVPI has got 308 ADR report from its various centres for Diclofenac injection 75 mg/ml annexed at 13. In majority of these reports more than one drug were administered. The causality assessments were possible / likely. In no case causality was assessed as certain. It is almost impossible to further delineate if the cause of ADR is attributable to excipient Transcutol-P®.

i) The committee was told that the use of parenteral Transcutol was not reflected in the website of the original supplier M/s Gattefosse when seen by the previous committee and this raised some concerns. It was informed and presented by M/s Gattefosse

representative that this was not put on the website because of commercial reason. However the information about parenteral use of Transcutol-P® has now been displayed in the company's official website. The printouts of website of Gattefosse for Transcutol P are annexed at-14.

j) The concern of the previous committee that US Pharmacopeia mentioned about the use of Transcutol in formulation other than parenteral was discussed. The committee is in agreement with the Indian Pharmacopoeia officials that monograph of the substance in the pharmacopoeia finds its mention if and when the particular product is marketed in that country. Since no parenteral formulation containing Transcutol-P® is marketed in USA, it may not find a mention in USP.

k) The committee also noted that DEGEE has been listed as an excipient for use in parenteral preparation in the 7th edition of the Hand book of Pharmaceutical Excipient (published by Pharmaceutical press, Wasington-DC) annexed at-15."

63. It is clear from the plain reading of the observations of the Second Committee, that the use of Transcutol P as an excipient required further examination by the concerned authorities.

64. This Court has certain reservations as to the approach of the Second Committee, as it may not have been apposite to permit the same if there were any reservations regarding the use of Transcutol P. Clearly, the reservations as to safety required are to be addressed prior to permitting the manufacture and sale of any drug. The concerned authorities had examined the report submitted by the Second

Committee and had decided to constitute a Review Committee (Third Committee). This was done by an order dated 03.05.2017, which is impugned herein.

65. It is contended on behalf of the petitioner that the constitution of the Third Committee is illegal and it was done at the behest of Troikaa. However, this Court finds no illegality in constitution of the Third Expert Committee. It is possible that the Committee was constituted on the complaints/representations made by Troikaa. However, the same does not render the decision to constitute the Third Committee as illegal. The decision whether the recommendations by a Committee required any further review is plainly at the discretion of the concerned authority. In the present case, the Second Committee had indicated that it has certain reservations even though it had concluded that the suspension of the drug in question was not warranted on safety concerns. It is contended on behalf of Troikaa that there is an inconsistency between the observations of the Second Committee and their conclusions drawn by it. However, it is not necessary to examine the said contention as it is apparent that the observations made by the Second Committee had struck certain cautionary notes insofar as the use of Transcutol P as an excipient is concerned and there is no infirmity in the decision of the concerned authorities to appoint a Committee to review the same.

66. The terms of reference of the Third Committee as set out in the order dated 03.05.2017 are reproduced below: -

"2. The Committee shall examine and assess:

(i) the claims and counter claims made with respect to the utility and toxicity of Transcutol-P in parenteral preparations based on available data and scientificknowledge;

(ii) whether there is sufficient evidence about the toxic effect of Transcutol-P which makes its use in parenteral preparations unsafe for human beings;

(iii) whether the existing parenteral preparations in the market containing Transcutol-P have toxicities which require banning of the products containing Transcutol-P; and

(iv) whether based on available evidence and the risk-benefit involved, Transcutol-P can be permitted forhuman use in parenteral formulations.

3. The Committee shall, after careful examination of the facts and available scientific evidence, make recommendations whether or not Transcutol-P is suitable for use inthe parenteral formulations."

67. The Third Committee had, after examining the facts, concluded as under: -

"Transcutol-P as an excipient in parenteral formulation needs to be tested for its toxicity independently in order to establish its safety; since it is reportedly not an inert excipient. No evidence has been presented before the Committee that it can be used in parenteral formulations even including India Pharmacopoeia, especially on parenteral preparation for human use.

> Like-wise, the data in cumulative form, is indicative of its toxicity which entails a detailed study on its toxicity and safety profile in line with the observations given above. Whether the same could be permitted for use especially in parenteral formulation has to be decided by Drug Regulatory Authority as per provisions of drug regulations on excipients to be used in parenteral form particularly those which are reportedly not inert, as in the present case."

68. The first and foremost question to be addressed is whether the decision-making process of the Third Committee was flawed. It was contended on behalf of the petitioner that (i) the Committee had failed to substantiate its finding by any reason or material; (ii) the decision was contrary to the minutes of the second meeting dated 12.07.2017 wherein opinion of the Toxicologist was recorded to the effect that the results of the studies presented by the petitioner did not show any adverse toxicity; (iii) the Committee had finalised its recommendations on 20.12.2017 in absence of a quorum on account of absence of three members, including the Toxicologist, and therefore, the recommendations made by the Third Committee were without jurisdiction; and (iv) that the decision of the Committee is in violation of principles of natural justice as no opportunity was afforded to Gattefosse to make any representation even though it was resolved in an earlier meeting that Gattefosse would be invited to make a representation.

69. The contention that the recommendations of the Third Committee were without jurisdiction as there was no quorum present on 20.12.2017, is erroneous and cannot be accepted. No quorum was

specified and merely because some members of the Committee were absent on one meeting, does not vitiate the decision of the Third Committee. The contention that there was no Toxicologist present on 20.12.2017 is also incorrect. The minutes of the meeting of the Third Committee held on 20.12.2017 indicates that Dr S. Raisuddin, Professor of Toxicology, Jamia Hamdard University, who was a member of the Committee, was present at the meeting held on 20.12.2017.

70. The petitioner's contention that the recommendations of the Third Committee made at its meeting held on 20.12.2017 is contrary to the opinion of the Toxicologist recorded at the meeting held on 12.07.2017 is also erroneous. The petitioner had relied upon the minutes of the meeting held on 12.07.2017 inasmuch as it had recorded the opinion of the Toxicologist to the effect that *"the results of studies presented by M/s Themis does not show any adverse Toxicity"*. However, the said observations must be read in their context. The said observations were made in the context of objections to the use of the Transcutol P as an excipient in the injectable product for clinical trials. The said observations were not made in the context of permitting the petitioner to manufacture and commercially market the drug in question using Transcutol P as an excipient. The permission to undertake clinical trials cannot be confused with the permission required for marketing a drug.

71. At this stage, it would be relevant to refer to the minutes of the meeting of the Third Committee held on 12.07.2017. The said minutes indicates that the Committee had heard the detailed representations

made by the petitioner as well as Troikka. Troikka had flagged various issues and also contended that DEGEE is metabolised in the body by Cyp-450 which converts DEGEE into Ethoxyethoxyacetic acid which Troikaa claimed, was a dangerous substance and harmful to kidney nephrons. Troikaa also claimed that the petitioner had obtained the license for manufacturing the drug in question from a State Licensing Authorities in violation of Rule 76(7) of the Rules.

72. The representation made by the petitioner were also noted by the Committee. The petitioner presented summary of the Toxicological studies conducted by it. After noting down the representations made by Troikaa and the petitioner, the Committee recorded its observations which are set out below:-

> "**Observation of the Expert Committee**
>
> After having heard both the parties, the Expert Committee discussed the points made by both the companies. Based on toxicity data on animals presented by M/s Themis, it was enquired by the Chairman whether the excipient can be allowed for clinical trial if any proposal w.r.t injectable preparation containing Transcutol-P was to be presented before the experts for granting permission for conducting Clinical Trial and subsequent uses in humans, will it be acceptable. Toxicologiests opined that the results of studies presented by M/s Themis does not show any adverse toxicity and safer doses are usually $1/10^{th}$ of NOAEL and in the present case, the firm has used 200mg in one vial to be used twice a day for 2 days only i.e. Daily exposure will be 400 mg only which is lesser than safety margin. Therefore, it is scientifically not objectionable to

use this excipient in injectable product for further clinical trials and subsequent uses. Further, the only issue remains after having being used this drug in millions of patients, the PvPI data of Diclofenac 75mg/3ml vs 75mg/ml containing Transcutol-P and other solubilizing agents, the comparative rate of Nephrotoxicity in these two kinds of formulations, then comparison of Novartis product with other 1 ml products using the denominator of number of patients exposed may provide some clue about the parttern of adverse reactions with regard to Nephrotoxicity. Therefore, the matter needs to be further deliberated in length.

Committee also discussed that Diclophenac drug itself has Nephrotoxicity, therefore, Nephrotoxicity due to Transcutol-P as an excipient in the parenteral formulation is not clear.

Committee further discussed and opined that all the claims and documents submitted presented by the both companies should be certified preferably by notarizing the same. M/S Gatefosse shall also be invited for making presentation before the Committee especially with respect to the toxicity data generated on Transcutol-P as well as data available with respect to the toxicity data generated on Transcutol-P as well as data available with respect to its metabolism for further robust evaluation. It needs to be ascertained about the international status regarding the availability of injections containing Transcutol-P. It also needs to be ascertained about the manufacturing method of Diclofenac injection containing Transcutol-P as use of autoclave at any step of the manufacturing may convert Transcutol-P.

> The Chairman requested the members to study the statements/claims made by both the firms and requested both the presenters to submit the legally valid documents preferably notarized w.r.t. statements and claims. As the Nephrotoxicity due to Transcutol-P is not clear, it was also opined that PvPI may be requested to analyse the Diclofenac 75mg/3ml injection 1ml, cases of Nephrotoxicity data for 3ml v 1ml, and also comparisons of incidences rate of Nephrotoxicity in formulations 1ml formulation containing Transcutol-P (i.e. Voveran 75mg/ml injection, Aquadol 75mg/ml injection) and others (i.e. other than 75mg/ml) vis a vis number of patients exposed if data is available. The data so collected shall be submitted to the Committee.
>
> The meeting ended with the vote of thanks to the chair."

73. It is apparent from the above observations that the Third Committee had also noted that it was necessary to ascertain the international status regarding availability of injections containing Transcutol P. It had also observed that Gattefosse would be invited for making a representation with regard to Toxicity data generated on Transcutol P for further robust evaluation.

74. The Chairman of the Third Committee also requested members to study the claims made by both the Firms.

75. It does appear that the Committee did not invite Gattefosse or undertake any further evaluation on the basis of any further analysis and made its recommendations on the basis of the representations made by Troikaa and the petitioner and the papers submitted by them. This is

clear from the letter dated 27.12.2017 addressed by the Chairman of the Third Committee to the Secretary, Ministry of Health and Family Welfare, Government of India informing him that the meetings of the Committee had been convened and the Committee had thoroughly discussed *"the matter on the basis of papers submitted by M/s Themis Medicare and M/s Troikka Pharmaceutical"*.

76. As is apparent from the plain language of the minutes of the meeting of the Third Committee held on 20.12.2017, the Expert Committee was of the view that there was no evidence presented before the Committee that Transcutol P could be used as an excipient in parenteral formulations. The Third Committee was of the view that the question whether Transcutol P could be permitted for use in parenteral formulation was required to be decided by the Drug Regulatory Authority as per the relevant provisions. The Chairman of the Third Committee also confirmed that the views of the Committee were in corroboration of the recommendations of the First Committee set up earlier. This Court is of the view that although the recommendations made by the Third Committee are not in detailed form, however, the same cannot be stated to be unreasoned. The Third Committee has clearly opined that they have found no evidence that Transcutol P could be used in parenteral formulations. It also noted that Transcutol P was not an inert substance and, therefore, the question whether the same could be approved for use in parenteral formulation was required to be decided by the Drug Regulatory Authority as per the relevant provisions.

77. Although the petitioner has sought to challenge the finding that Transcutol P is an inert substance, it has not produced any material to establish that Transcutol P is an inert substance. It had merely referred to the handbook of pharmaceutical excipient and had relied upon the statement contained therein that DEGEE "is generally regarded as non-irritant and non-toxic". This is, plainly, not the same as being inert which would imply that the substance is chemically inactive.

78. It is relevant to note that the Expert Committee also observed that it was necessary to ascertain the international status regarding availability of injections containing Transcutol P. It was contended that no material had been produced before the Committee to establish that Transcutol P was used as an excipient in parenteral form in other nations. In this regard, this Court, by an order dated 27.07.2018, had directed respondents to file an affidavit indicating where Transcutol P is used or permitted in parenteral form in the following developed countries "United States of America, United Kingdom, Germany and Australia". In compliance with the said directions, an affidavit was filed on behalf of respondent nos. 1 and 5 conforming that Transcutol P was not approved for use in the parenteral form in United States of America, Canada, Australia. In the said countries, DEGEE was permitted only for toxical use and not in parenteral form. It was further affirmed that the usage of Transcutol P in parenteral formulation was not found as searched from the official website in United Kingdom. Insofar as the European Union (EU) is concerned, it was affirmed that the Scientific Committee on Consumer Safety had given an opinion on 26.02.2013

that the use of DEGEE with certain limits of concentration is permissible in cosmetic products. It was also clarified that aggregate exposure to DEGEE from non-cosmetic sources was not considered by the Scientific Committee. Insofar as the France is concerned, it was affirmed as under:-

> "French agency for safety of health product (AFSSAPS) has suspended the marketing authorization for the medicinal product PILOSURYL containing Transcutol implicated in the occurrence of serious side effects, kidney and neurological damage. The use of UROSIPHON that contains same excipient Transcutol, was suspended as a precautionary measure."

79. In view of the above, this Court finds no infirmity in the decision-making process of the Third Committee in recommending that the question whether Transcutol P is required to be permitted in a parenteral formulation must be decided by the Drug Regulatory Authority as per provisions of Regulations on excipient to be used in parenteral form.

80. At this stage, it is relevant to refer to Sub-rule (7) of Rule 76 of the said Rules, which reads as under:-

> "76.[Forms of licence to manufacture drugs specified in Schedules C and C(1), [excluding those specified in Part XB and Schedule X], or drugs specified in Schedules C, C(1) and X and the conditions for the grant or renewal of such licences.- A licence to manufacture for sale or for distribution of drugs specified in Schedules C and C(1) other than 4 [Large Volume Parenterals, Sera and Vaccine and Recombinant DNA (r-DNA) derived drugs] specified in Part X B and Schedule X shall be issued in Form 28 and a licence to manufacture for sale or distribution of drugs

specified under Schedules C and C(1) (other than 4 [Large Volume Parenterals, Sera and Vaccine and Recombinant DNA (r-DNA) derived drugs] specified in Part X-B) and Schedule X shall be issued in Form 28B. A licence to manufacture for sale or for distribution of 4 [Large Volume Parenterals, Sera and Vaccine and Recombinant DNA (r-DNA) derived drugs] shall be issued in Form 28-D. Before a licence in Form 28 or Form 28B or Form 28D is granted or renewed, the following conditions shall be complied with by the applicant:-

xxxx xxxx xxxx xxxx

(7) The applicant shall, while applying for a licence to manufacture patent or proprietary medicines, furnish to the licensing authority evidence and data justifying that the patent or proprietary medicines-

(i) contain the constituent ingredients in therapeutic/ prophylactic quantities as determined in relation to the claims or conditions for which the medicines are recommended for use or claimed to be useful;
(ii) are safe for use in the context of the vehicles, excipients, additives and pharmaceutical aids used in formulations, and under the conditions in which the formulations for administration and use are recommended;
(iii) are stable under the conditions of storage recommended; and
(iv) contain such ingredients and in such quantities for which there is therapeutic justification.
(v) have the approval, in writing, in favour of the applicant to manufacture drug formulations falling under the purview of new drugs as defined in rule 122-E, from the licensing authority as defined in clause (b) of rule 21."

81. The onus of establishing that Transcutol P is safe for use in parenteral form rests on the petitioner and the petitioner is required to discharge the same. It cannot be assumed that Transcutol P is safe unless proven otherwise. The approach of the petitioner that use of Transcutol P must be accepted to be safe unless established to the contrary by the respondents, is flawed.

82. It is material to note that the petitioner had obtained the license to manufacture the drug in question on the basis that it was not a new drug. This was considering the fact that Troikaa was granted the approval to manufacture the drug in question under Rule 122B and 122E of the said Rules way back on 30.07.2007. However, it is not disputed that the drug in question manufactured by Troikaa does not use Transcutol P as an excipient. Thus, the drug manufactured by Troikaa using Transcutol P as an excipient has never been approved by the DCGI.

83. It was contended on behalf of the petitioner that while applying for a license to manufacture the drug in question, it had provided the necessary evidence and data justifying that the use of the drug in question was safe in the context of the excipient Transcutol P. This was contested by the respondents and it was submitted that the petitioner had obtained the license to manufacture the drug in question based on the approval granted to Troikka earlier. There is no material on record indicating that the petitioner had presented data justifying that the use of excipient Transcutol P is safe while applying for the license to manufacture the drug in question. On the contrary, it is the petitioner's

assertion that the drug in question was not a new drug and, therefore, the petitioner was granted license to manufacture the same by the State Drug Licensing Authorities.

84. The next question to be examined is whether the decision of the Third Committee is vitiated on account of not affording Gattefosse an opportunity to be heard. This Court is unable to accept that Gattefosse had any right to be heard by the Third Committee. The Third Committee has not returned any finding whether Transcutol P was unsafe in parenteral preparations. It had merely recommended that the question whether the same ought to be permitted would require to be decided by the Regulatory Authority in accordance with law. The question whether Transcutol P could be used as an excipient was required to be established by the petitioner being the entity which had sought license to manufacture the drug in question using the excipient. Gattefosse had neither sought nor was granted any approval from the Authority. It is also relevant to note that Gattefosse is a foreign company and does not enjoy any right under Article 19(1)(g) of the Constitution of India.

85. Although, the Third Committee had a meeting held on 12.07.2017 observed that Gattefosse would be invited to make a representation, however, it had subsequently submitted a report based on the documents submitted by Troikaa and the petitioner and this was clearly indicated in the letter dated 27.12.2017 sent by the Chairman of the Third Committee forwarding its recommendations.

86. It was also contended on behalf of the petitioner that the recommendation of the Third Committee was flawed as it had not addressed the terms of reference. The Third Committee was constituted by an order dated 03.05.2017 to, *inter alia,* examine and assess whether there was sufficient evidence about the toxic effect of Transcutol P which made it unsafe for use in parenteral preparation and whether use of Transcutol P in parenteral preparation were required to be banned. The Committee was also to assess whether Transcutol P could be permitted for human use. Clearly, the Committee was unable to answer the said issues as it found that there was lack of sufficient evidence and material for it to do so. However, it concluded that there was a requirement to test Transcutol P as an excipient for its toxicity independently to establish its safety. Thus, while it is correct that the Third Committee did not answer the issues raised, nonetheless, its recommendations cannot be faulted. It is also relevant to note that the Committee was not formed under any statute and its recommendations do not have a statutory flavour. The Third Committee was constituted merely as an expert committee to submit its recommendations to the regulatory authorities.

87. The communication sent by the DCGI to Drug Licensing Authorities of the State of Uttarakhand and the Union Territory of Daman and Diu cannot be faulted. DCGI had called upon the said Drug Licensing Authorities to cancel the license granted to the petitioner to manufacture the drug in question, as the drug in question using Transcutol P as an excipient had not been approved as per the Rules.

88. In view of the above, this Court finds no merit in the present petitions. The same are dismissed.

89. All pending applications are disposed of.

VIBHU BAKHRU, J

JULY 5, 2019
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