To

The Controller of Patents,

The Patent Office at Delhi

Re. **Opposition under Section 25(1) against**

Patent Application No. 202118039376 dated 31/08/2021

Applicant: ELI LILLY AND COMPANY

Opponent: Dr. C. Manivannan

Dear Sir,

This letter is in reference to submission of 'Pre-Grant Opposition' under section 25(1) of the Indian Patents Act 1970 concerning patentability of invention on the issue of 'Inventive Step' of the claims among other grounds against Patent Application No. 202118039376 dated 31/08/2021 titled: "GIP/GLP1 AGONIST COMPOSITIONS" of whose the Applicant is ELI LILLY AND COMPANY.

In view of the above, Pre-Grant Opposition along with the relevant form and documents is being enclosed for your kind consideration.

Thanking you.

Dated: 17th January 2024

Yours faithfully,

Mr. Tarun Khurana
IN/PA/1325
Of Khurana and Khurana Advocates and IP Attorneys
(Agent of the Opponent)
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BEFORE THE CONTROLLER OF PATENTS

DELHI

REPRESENTATION FOR OPPOSITION TO GRANT OF PATENT UNDER SECTION 25(1) OF THE PATENTS ACT, 1970 AGAINST PATENT APPLICATION NO. 202118039376 DATED AUGUST 31, 2021

Dr. C. Manivannan of 3A, Chinna Andaar Street, Kulithalai (TK), Karur (Dt), Tamil Nadu - 639104, India

……Opponent

-VS-

ELI LILLY AND COMPANY [Nationality-US] of Lilly Corporate Center Indianapolis, Indiana 46285, US

……Applicant

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BEFORE THE CONTROLLER OF PATENTS

DELHI

In the matter of Section 25(1) of The Patents Act, 1970 as amended by The Patents (Amendment) Act 2005;

And

In the matter of The Patents (Second Amendment) Rules 2006

And

IN THE MATTER of Indian Patent Application No. 202118039376 dated 31/08/2021 in the name of ELI LILLY AND COMPANY of Lilly Corporate Center Indianapolis, Indiana 46285, US

…….. Applicant

And

IN THE MATTER of representation by way of opposition to grant of patent thereto by Dr. C. Manivannan of 3A, Chinna Andaar Street, Kulithalai (TK), Karur (Dt), Tamil Nadu - 639104, India

…… Opponent

STATEMENT OF CASE FOR REPRESENTATION UNDER SECTION 25(1) OF THE PATENTS ACT 1970

I. THE OPPONENT

1. The Opponent herein is Dr. C. Manivannan of 3A, Chinna Andaar Street, Kulithalai (TK), Karur (Dt), Tamil Nadu - 639104, India. The Opponent is an individual with a Doctoral degree in Chemistry and has over 15 years of academic and research experience in the field of chemistry, life sciences and pharmaceuticals.

II. THE INDIAN PATENT APPLICATION NO. 202118039376

2. The Patent Application No. 202118039376 (hereinafter referred to as "the impugned application") entitled "GIP/GLP1 AGONIST COMPOSITIONS" was filed in India on Aug. 31, 2021 as a divisional application to parent application No. 202017050717. The impugned application was filed from the PCT International Application No. PCT/US2019/037146 dated June 14, 2019 which in turn claimed priority of June 22, 2018. The impugned application was published in the official journal of the Indian Patent Office on Feb. 11, 2022.

3. The impugned application was filed in India with 35 claims broadly covering pharmaceutical compositions of tirzepatide or a pharmaceutically acceptable salt thereof, comprising an agent selected from the group consisting of NaCl and propylene glycol; and dibasic sodium phosphate. The complete specification of the impugned application as obtained from the inPASS (Indian Patent Advanced Search System) database made available by the Indian Patent Office on its official website is attached herein as **Annexure I**.

4. The Indian Patent Office issued First Examination Report (F.E.R.) on June 30, 2023. The Applicant submitted its response to the F.E.R. on Nov. 06, 2023 along with an amended set of 1-15 claims, attached herewith as **Annexure II**. This set of amended claims 1-15 (latest/current) is being challenged by way of this pre-grant opposition.

5. According to the Patent Office website the impugned application is not yet granted. The current status of the impugned application is “Reply Filed. Application in amended examination”.

II.1 CLAIMS (LATEST/CURRENT) OF THE IMPUGNED APPLICATION

6. The claims below represent the amended set of 1-15 claims filed by the Applicant on Nov. 06, 2023 in respect of the impugned application in response to the F.E.R.

1. A pharmaceutical composition comprising
tirzepatide, or a pharmaceutically acceptable salt thereof;
propylene glycol; and
dibasic sodium phosphate.

2. A pharmaceutical composition as claimed in Claim 1 wherein the tirzepatide, or a pharmaceutically acceptable salt thereof, concentration is from 5 to 30 mg/mL.

3. A pharmaceutical composition as claimed in Claim 2 wherein the dibasic sodium phosphate concentration is from 1.0 mg/mL to 3.0 mg/mL.

4. A pharmaceutical composition as claimed in Claim 1 wherein the dibasic sodium phosphate concentration is from 0.67 mg/mL to 2.68 mg/mL.

5. A pharmaceutical composition as claimed in Claim 4 wherein the dibasic sodium phosphate concentration is 1.34 mg/mL.

6. A pharmaceutical composition as claimed in Claim 1 wherein the tirzepatide, or a pharmaceutically acceptable salt thereof, concentration is selected from the group consisting of 5, 10, 15, 20, 25, and 30 mg/mL.

7. A pharmaceutical composition as claimed in Claim 6 wherein the tirzepatide, or pharmaceutically acceptable salt thereof, concentration is selected from the group consisting of 10, 20, and 30 mg/mL.

8. A pharmaceutical composition as claimed in Claim 1 wherein the concentration of propylene glycol is from 12.0 mg/mL to 18.0 mg/mL.

9. A pharmaceutical composition as claimed in Claim 8 wherein the concentration of propylene glycol is from 14.0 mg/mL to 16.0 mg/mL.

10. A pharmaceutical composition as claimed in Claim 9 wherein the concentration of propylene glycol is 15.0 mg/mL.

11. A pharmaceutical composition as claimed in Claim 1 wherein tirzepatide, or pharmaceutically acceptable salt thereof, concentration is from 5 mg/mL to 30 mg/mL; dibasic sodium phosphate concentration is from 0.67 mg/mL to 2.68 mg/mL; and propylene glycol concentration is from 14.0 mg/mL to 16.0 mg/mL.

12. A pharmaceutical composition as claimed in Claim 11 wherein tirzepatide, or pharmaceutically acceptable salt thereof, concentration is from 5 mg/mL to 30 mg/mL; dibasic sodium phosphate concentration is 1.34 mg/mL; and propylene glycol concentration is 15.0 mg/mL.

13. A pharmaceutical composition as claimed in Claim 12 wherein the composition is presented in an automatic injection apparatus.

14. A pharmaceutical composition as claimed in Claim 1 wherein the pH of the composition is from 6.5 to 7.5.

15. A pharmaceutical composition as claimed in Claim 14 wherein the pH is from 6.7 to 7.3.

III. GROUNDS OF OPPOSITION

7. The Opponent submits that the impugned application is invalid and therefore grant of patent ought to be refused. The opponent relies upon the following grounds in the instant pre-grant opposition:

i. **Section 25(1)(e)**– that the invention claimed in the impugned application is obvious and clearly does not involve any inventive step.

ii. **Section 25(1)(f)**– that the subject of any claim of the complete specification is not an invention within the meaning of this act or is not patentable under this act.

iii. **Section 25(1)(g)**– that the complete specification of the impugned application does not sufficiently and clearly describe the invention or the method by which it is to be performed.

IV. PRIOR ART RELIED UPON

Document	Patent No. / Article	Publication Date/Year
D1	US 9474780 B2. Annexed herein as **Annexure III**	Oct. 25, 2016
D2	WO 2003/002136 A2. Annexed herein as **Annexure IV**	Jan. 09, 2003
D3	US 8114833 B2. Annexed herein as **Annexure V**	Feb. 14, 2012
D4	WO 2016/038521 A1. Annexed herein as **Annexure VI**	March 17, 2016
D5	YU et al, "Pain perception following subcutaneous injections of citrate-buffered and phosphate-buffered epoetin alpha", The International Journal of Artificial Organs / Vol. 21 / no. 6, 1998 / pp. 341-343. Annexed herein as **Annexure VII**	1998

V. THE PERSON SKILLED IN THE ART

8. A person skilled in the art at the time of earliest filing date of the impugned application would have had at least a Bachelor's degree in pharmaceutical science with several years' experience in pharmaceutical formulations and dosage form design and development, or alternatively, an advanced degree (Masters or Ph.D.) in pharmaceutical science or pharmacy with emphasis in these same areas. This person may also work in collaboration with other scientists and/or clinicians who have experience in diabetology, or related disciplines.

VI. OBVIOUSNESS / LACK OF INVENTIVE STEP [Section 25(1)(e)]

9. The Opponent states that the subject-matter of claims 1-15 of the impugned application lacks inventive merit and is obvious to a person skilled in the art in view of the prior art documents annexed in the instant pre-grant opposition.

VI.1 Claim 1 lacks inventive step in view of D1 combined with the teachings of D2 to D5

10. Claim 1 of the impugned application is directed to a pharmaceutical composition comprising:

    tirzepatide, or a pharmaceutically acceptable salt thereof;
    propylene glycol; and
    dibasic sodium phosphate.

    The experimental examples of the specification of the impugned application disclose tirzepatide injectable compositions according to instant claim 1 (see, Tables 5, 6, 7 and 8 of the impugned application) that are alleged to provide desired shelf-life stability and acceptable patient injection site experience.

11. **D1** (US9474780B2) discloses dual incretin peptide mimetic compounds that agonize receptors for both GIP and GLP-1, and are useful for treating type 2 diabetes mellitus (see, abstract). Specifically, **D1** discloses and claims tirzepatide, which is the specific dual GIP and GLP-1 receptor agonist, as defined in claim 1 of the impugned application

(see, claim 15 at column 44 of D1). **D1** also discloses in claim 16 a pharmaceutical composition comprising tirzepatide as active ingredient together with a pharmaceutically acceptable carrier, diluent, or excipient. **D1** further discloses a method of treating type 2 diabetes mellitus in a patient by administering a pharmaceutical composition comprising tirzepatide (see, claim 17 of D1).

12. While D1 discloses a pharmaceutical composition comprising tirzepatide as active ingredient, D1 does not explicitly disclose a composition of tirzepatide comprising propylene glycol and dibasic sodium phosphate as recited in instant claim 1.

13. However, the use of propylene glycol and dibasic sodium phosphate in peptide-containing pharmaceutical formulations is commonly known, and also suggested for liquid parenteral formulations comprising glucagon-like peptides, see, e.g., documents **D2** to **D4**. Documents **D2** to **D4** are concerned with the same field of aqueous parenteral pharmaceutical compositions (e.g., subcutaneous injections) comprising glucagon-like peptides. These documents provide formulations that are formulated in a way to improve the physical and chemical stability of the formulations.

14. The skilled person would learn from **D2** (WO2003002136A2) that therapeutic proteins (peptides) are typically unstable and are susceptible to both chemical and physical degradation (see, D2, page 2, lines 12-24). He would also learn from **D2** that such peptide instability can be avoided by providing peptide compositions comprising an isotonic agent (e.g. **propylene glycol**) and a buffer (e.g. disodium hydrogen phosphate, also known as **dibasic sodium phosphate**) (see, D2, page 37, lines 12-21, "Example 1"; page 17, lines 27-33; and page 18, lines 33-35). Further he would learn that the concentration of said therapeutic peptide in the composition can range from 1 mg/ml to 80mg/ml, preferably from 1 mg/ml to 20mg/ml (see, page 18, lines 1-6), and that the concentration of said isotonic agent can be from 1 mg/ml to 50 mg/ml, preferably from 8 mg/ml to 16 mg/ml (see, page 19, lines 10-13).

15. From **D3** (US8114833B2) the skilled person would learn that shelf-stable formulation of therapeutic peptides is obtained by a pharmaceutical composition comprising a therapeutic peptide, **propylene glycol (isotonic agent)** and disodium phosphate

dihydrate buffer (=**dibasic sodium phosphate** buffer) (see, column 1, lines 53-60, and claim 1 at column 22). He would also learn from **D3** that propylene glycol can present in the formulation in a concentration of from about 8 mg/ml to 16 mg/ml, and that the pH of the formulation can range from about 7.0 to about 10.0 (see, claims 1 and 4 at column 22).

16. The skilled person would learn from **D4** (WO2016038521A1) that in order to improve stability of the peptide liraglutide, a pharmaceutical formulation of a peptide may comprise **propylene glycol** and disodium phosphate buffer (=**dibasic sodium phosphate** buffer) (see, **D4**, claims 1 and 4 at page 7). He would also learn from **D4** that therapeutic peptide can present in the formulation in a concentration of 6.43 mg/mL, that the propylene glycol can present in the formulation in a concentration of 14 mg/mL, and that the disodium phosphate buffer can present in a concentration of 1.12 mg/mL (see, **D4**, Example 3 at page 5). By further reading **D4**, skilled person would learn that the pH of peptide formulation can range from about 7.0 to about 10.0 (see, page 3, lines 18-19).

17. From **D5** (YU et al.) the skilled person would learn that phosphate-buffered drug formulations reduce injection-site pain associated with subcutaneous injection in patients (see, **D5**, abstract, and page 343, left-column, lines 9-11). Dibasic sodium phosphate is disclosed in **D5** as a prominent example of a phosphate buffer (see, page 341, right-column, lines 3-4).

18. Therefore – taking into account the disclosure of document **D1** with respect to pharmaceutical composition of tirzepatide and given the teachings of **D2 to D4** that shelf-stable formulation of therapeutic peptides can be obtained by a pharmaceutical composition comprising therapeutic peptide, propylene glycol as isotonic agent and dibasic sodium phosphate as buffer – the provision of a composition of tirzepatide, comprising propylene glycol and dibasic sodium phosphate is not based on any inventive activity, and does not constitute an inventive contribution to the art. The skilled person would be motivated by the teaching of **D2** to **D5** to include propylene glycol and dibasic sodium phosphate into the pharmaceutical composition of tirzepatide as disclosed in **D1** in order to obtain pharmaceutical compositions having prolonged stability during storage and providing acceptable patient injection site experience. In order to arrive at effective

formulations, he would further adopt the concentrations of propylene glycol, dibasic sodium phosphate and the pH of formulation as suggested by **D2** to **D4** by routine experimentation, if at all required. By doing that, he would inevitably arrive at the claimed invention.

19. Accordingly, the independent claim 1 lacks inventive step in view of **D1** combined with the teaching of **D2** to **D5**.

VI.2 Claims 2 to 15 lack inventive step in view of D1 combined with the teachings of D2 to D5

20. As already outlined above, pharmaceutical composition comprising tirzepatide, propylene glycol and dibasic sodium phosphate is obvious and does not involve an inventive step in view of D1 combined with the teachings of D2 to D5. The Opponent states that the dependent claims 2 to 15 also do not involve an inventive step, because varying the amounts of excipients represents however a usual procedure for a skilled person and does not involve an inventive step. This applies in particular when these excipients are merely used in usual amounts well known to a skilled person and in absence of any surprising effects associated with such excipient variations:

- **Propylene glycol** is known to be used in liquid parenteral formulations in the range between 8-16 mg/ml (see, **D3**, claims 1 and 4 at column 22)

- **Therapeutic peptides** are known to be present in liquid parenteral formulations from 1 mg/ml to 80mg/ml, preferably from 1 mg/ml to 20mg/ml (see, **D2**, page 18, lines 1-6)

- Peptide-containing parenteral formulations are known to have **pH** in the range of 7.0 to 8.3 (see, **D3**, claim 6 at column 22)

21. Thus, also the subject-matter of claims 2 to 15 of the impugned application lacks an inventive step in view of **D1** combined with the teachings of **D2** to **D5**.

22. For the reasons set forth above, it is therefore respectfully submitted that the subject-matter of claims 1 to 15 of the impugned application is obvious and does not meet the

requirements with regard to inventive step, and as such is not patentable under the provisions of Section 25(1)(e) read with Section 2(1)(ja) of the Patents Act.

VII. NOT AN INVENTION/ NOT PATENTABLE [Section 25(1)(f)]

23. Section 25(1)(f) of the Patents Act, 1970 governs the case where the subject of any claim of the complete specification is not an invention within the meaning of this act, or is not patentable under this act.

Not an Invention / Not Patentable u/s 3(e)

24. The subject-matter of claims 1-15 of the impugned application is squarely covered by Section 3(e) in light of the submissions below.

> Section 3(e) of the Indian Patent Act bars patentability of a subject-matter wherein the subject-matter is *"a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance"*.

25. As shown above, the composition comprising tirzepatide, propylene glycol and dibasic sodium phosphate is wholly obvious and lacks an inventive step. The Opponent further states that the claimed tirzepatide composition is not patentable within the meaning of Section 3(e) of the Patents Act as the composition does not exhibit any unexpected or surprising effect.

26. During the examination proceedings, the Applicant argued that a composition comprising tirzepatide, propylene glycol and dibasic sodium phosphate provides a desired shelf-life stability and acceptable in-use stability, and hence the present claims do not attract Section 3(e) of the Patents Act. The Opponent disagrees. As discussed in detail supra, document **D1** discloses a pharmaceutical composition comprising tirzepatide (see, claims 15 and 16 of D1). As already outlined above, it was known from documents **D2 to D4** that shelf-stable formulation of therapeutic peptides can be obtained by a pharmaceutical composition comprising therapeutic peptide, propylene glycol and dibasic sodium

phosphate buffer. Consequently, there is no doubt that at the priority date of the impugned application the person skilled in the art was perfectly aware of the suitability of propylene glycol and dibasic sodium phosphate for use in pharmaceutical compositions improving the physical and chemical stability of respective therapeutic peptides. Thus, the improved stability of the claimed composition is an obvious result, which the person skilled in the art will achieve when plainly and logically following the teachings of the cited prior arts. Hence, the composition as claimed is nothing but a combination of known components exhibiting a mere aggregation of known, expected properties and no unexpected effect is evident. It is therefore asserted that the claimed composition is clearly hit by Section 3(e) of the Patents Act, 1970 and does not form a patentable invention under the Act.

27. The Opponent therefore humbly implores that the impugned application be rejected under this ground alone.

VIII. INSUFFICIENT DISCLOSURE [Section 25(1)(g)]

28. **Lack of enablement of claim 1**: The Opponent states that the independent Claim 1 does not sufficiently define the alleged invention and it is very broad in nature. Claim 1 of the impugned application is directed to a pharmaceutical composition comprising tirzepatide, propylene glycol, and dibasic sodium phosphate. The claim 1 does not place any limit on the amount of tirzepatide, propylene glycol and dibasic sodium phosphate that can be present. The examples in the specification of the impugned application disclose compositions containing tirzepatide, propylene glycol, and dibasic sodium phosphate in defined amounts. Specifically, the specification (on page 9, Tables 5, 6) alleges that compositions containing 20 mg/ml of tirzepatide, 1.34 mg/ml of dibasic sodium phosphate and 15 mg/ml of propylene glycol provide acceptable shelf-life stability. Similarly, it is alleged (on pages 10-11, Tables 7, 8) that a composition containing 20 mg/ml of tirzepatide, 1.34 mg/ml of dibasic sodium phosphate and 15 mg/ml of propylene glycol provides patients with an acceptable injection site experience. Such amounts imperative to the operability of the composition are, however, not recited in the independent claim 1, which in its current wording could contain the ingredients in any amount without limitation. This either implies that the alleged invention cannot be

carried out over the whole breadth of claim 1, or indicates that claim 1 does not comply with the requirements set forth in section 10 (4) of the Patents Act, 1970.

29. It is respectfully submitted that upon detailed and careful analysis of the impugned application, several lacunae, infirmities, defects, insufficiencies and ambiguities are borne out. It is for this reason that the opponent has established various grounds of opposition under section 25(1) and the impugned application is therefore ought not to be granted.

IX. RELIEF SOUGHT

30. The Opponent states that it has established and made out a case on each of the aforesaid grounds of opposition and pray to the Learned Controller for the following relief(s):

(a) Take on records the present representation

(b) Leave to file further evidence

(c) Opportunity to be heard

(d) Refusal of the 202118039376 application *in toto*

(e) Such other relief(s) as the Learned Controller may deem appropriate.

31. The opponent requests for a Personal Hearing before the Controller of Patents, before a decision adverse to the Opponent is taken in this matter.

Dated this 17th day of January 2024

Mr. Tarun Khurana
IN/PA/1325
(Agent of the Opponent)

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To
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