2025:MHC:2096

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IN THE HIGH COURT OF JUDICATURE AT MADRAS

Judgment reserved on	**17.07.2025**
Judgment pronounced on	**22.08.2025**

CORAM:

THE HON'BLE MR. **JUSTICE SENTHILKUMAR RAMAMOORTHY**

CMA (PT) No.28 of 2023

AMGEN INC.
Patent Operations M/S 28-2
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
The United States of America ... Appellant

v.

1. THE ASSISTANT CONTROLLER OF PATENTS
AND DESIGNS
The Patent Office
Intellectual Property Building,
G.S.T. Road, Guindy, Chennai-600 032.

2. INTAS PHARMACEUTICALS LIMITED
2nd Floor, Chinubhai Centre,
Ashram Road, Ahmedabad
Gujarat-380 009. ... Respondents

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PRAYER: This Civil Miscellaneous Appeal (Patent) filed under Section 117 A of the Patents Act, 1970, praying that this Court may be pleased to:

a. Allow the present appeal and pass an order setting aide the impugned order dated 31.03.2023 wherein it has been held that claims 1-13 of the Patent Application no.5857/CHENP/2008 are not patentable under Section 2(1)(ja), 3(d), 3(e) and 10(4) of the Act.

b. Pass an order granting a patent on the Indian Patent Application No.5857/CHENP/2008 and issue consequential directions to effectuate such grant; in any case hold the invention is patentable, and a patent be granted for these claims and issue consequential directions to effectuate such grant.

For Appellant : Ms.Vindhya S. Mani
Mr.Sheerabdhinath
Mr.Kiran Manokaran
for M/s.Lakshmi Kumaran and
Sridharan Attorneys

For Respondent : Mr.S.Majumdar
Mr.Dominic Alvares
Mr.Mitul Das Gupta
for M/s. P. Arul Gnana Prakash & S.Akash
for R2
Mr.A.R.Sakthivel for R1
Ms.Resmi C. Senan,
Assistant Controller (Present on VC)

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JUDGMENT

Introduction

As with most patent cases, in this case too, an understanding of the basic science and terminology relevant to the claimed invention is vital for effective adjudication. Therefore, by way of this introduction, I have attempted to explain the science and terminology to the extent understood by me.

2. Allopathic drugs were typically synthesized from chemicals. It was discovered later that certain conditions and disorders could be treated effectively by developing drugs that trace their origin from biological sources. Therefore, drugs were developed from human, animal, plant or even microbial sources. The primary ingredient of these drugs is a protein, peptide, enzyme, antibody, toxin or other biological material. Such drugs are referred to as biologics or biopharmaceuticals. The primary therapeutic ingredient in any drug, whether of chemical or biological origin, is called the active pharmaceutical ingredient (API). Along with the API, other

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ingredients called excipients are used in all drugs to produce a pharmaceutical formulation that may be administered to humans or animals through one or more modes of drug delivery/administration. Because these excipients do not have a direct pharmacological action, they are often referred to as inactive ingredients. Another aspect to be borne in mind with regard to the formulation of biologics is that, at present, unlike chemical drugs, they cannot be administered orally in the form of tablets, capsules, syrups, etc. Instead, they are intended to be administered by parenteral modes. This expression has a wide ambit and covers administration of drugs otherwise than through the mouth and alimentary canal/digestive system. Therefore, it would include administration through modes such as intramuscular, intravenous and subcutaneous.

3. Protein is made of amino acids and a relatively short protein chain or sequence is called a peptide. The United States Food and Drug Administration (the FDA) defines a peptide as a chain of amino acids containing a maximum of 40 monomers or less. There are

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about twenty amino acids. Both in naturally occurring and synthetic peptides, these amino acids could be present in different permutations and combinations resulting in a vast variety of sequences. One of the problems encountered with the administration of biologics, including peptide therapeutics, is immunogenicity or resistance by the human body by *inter alia* producing antibodies in response. This problem was found to be mitigated by producing synthetic or engineered peptides through recombinant DNA technology that mimic the functions of the corresponding natural protein, but are not homologous. Such synthetic peptides are called peptide mimetics. In comparison to the molecules of drugs synthesized from chemicals, protein molecules are large and inherently unstable outside their natural environment. Consequently, they are prone to both physical and chemical degradation.

4. In order to improve the stability of not only pharmaceutical but even food products, especially during storage and transportation, including by preventing aggregation, they are often freeze-dried. This

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process is called lyophilization and involves freezing, primary drying and secondary drying. During the primary drying stage, water is removed from the frozen sample by a process called sublimation, i.e. conversion from solid to gaseous state. A process called desorption is followed at the secondary drying stage to remove the remaining water. Especially in view of the instability referred to in the preceding paragraph, lyophilization is often resorted to in the context of biologics.

5. For purposes of *inter alia* improving stability during freeze-drying, storage, transportation and administration, excipients are added to the API. An excipient used to protect the API during the freezing phase is called a cryoprotectant and an excipient used for the same purpose during the drying phase is called a lyoprotectant. On the basis of functions, excipients used in biologics may be categorised *inter alia* as stabilizers, lyo/cryoprotectants, buffering agents, bulking agents, surfactants, tonicity agents, pH adjusting agents, solubilizing agents, anti-microbial preservative and anti-adhesive

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agents. It should also be borne in mind that an excipient could perform more than one function in a formulation. Typically, excipients form the bulk of the formulation in comparison to the API.

6. Platelets play a significant role in the blood clotting process. Thrombopoietin (TPO) is a hormone that stimulates the production of platelets in the human body. In certain conditions, such as immune thrombocytopenic purpura (ITP), natural platelet production is affected. As a measure to address this problem, the appellant had earlier made an engineered peptide that displaces TPO from its receptor (TPOR or c-MPL). Any substance that initiates a physiological response when combined with a receptor is called an agonist. Since this peptide stimulates the TPO receptor, it is called a TPOR agonist (TPO-RA). One of the drawbacks of administering therapeutic peptides is that they are cleared rapidly by the human kidney during micturition/urination and, consequently, do not remain in the body long enough to provide therapeutic benefit.

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7. Every antibody is a Y-shaped structure with two fragment antigen binding (Fab) regions at the upper end and a fragment crystallizable (Fc) region at the tail end. The Fab regions bind to the antigen and are variable, whereas the Fc region is constant and interacts with the Fc receptors. In order to deal with the rapid clearance problem, the appellant grafted the above mentioned engineered peptide on the Fc region of the human immunoglobulin antibody (IgG). The fused entity was called a peptibody by the appellant, and a patent was granted in other jurisdictions. The FDA approved the API formulation, which is called romiplostim, for therapeutic use and the same is marketed as Nplate.

Background to the appeal

8. Lyophilized formulations were prepared by the appellant by adding specific excipients in specific concentrations to the active ingredient/peptibody. An application, No.5857/CHENP/2008, for grant of patent for such lyophilized formulations titled "LYOPHILIZED THERAPEUTIC PEPTIBODY FORMULATIONS"

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was filed. This application was rejected by order dated 31 March 2023, which is impugned herein.

9. After filing the above mentioned application, the appellant requested the first respondent to examine the same. On 20 July 2013, the first respondent issued the First Examination Report (FER) wherein objections were raised *inter alia* on grounds that claim 1 and its dependent composition claims fall within the scope of Section 3(d) and 3(e) of the Patents Act, 1970 (the Patents Act); and claims 1 to 81 lack an inventive step with respect to prior arts D1 to D6. The appellant submitted a partial response to the FER on 16 December 2013 and a complete response on 25 July 2014. After receiving hearing notice dated 27 April 2016, the appellant filed written submissions on 24 June 2016.

10. At that juncture, the second respondent filed a pre-grant opposition on 18 July 2016. The pre-grant opposition was filed on the following grounds: the claimed invention is obvious and does not

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involve an inventive step [Section 25(1)(e) of the Patents Act, 1970 ('Patents Act')]; the claimed invention is not an invention within the meaning of the Patents Act or is not patentable [Section 25(1)(f)]; and the claimed invention does not sufficiently and clearly describe the invention or the manner in which it is to be performed [Section 25(1)(g)]. The appellant replied to the pre-grant opposition on 21 December 2016. Hearing notices were issued thereafter and eventually the hearing took place on 8 December 2020. After the hearing, the appellant filed written submissions on 25 December 2020. The order impugned herein was issued in the above facts and circumstances.

Counsel and their contentions:

11. Ms.Vindhya S. Mani, learned counsel, appeared on behalf of the appellant. Mr.S.Majumdar, learned counsel, assisted by Mr.Dominic Alvares, learned counsel, appeared on behalf of the second respondent and Mr.A.R.Sakthivel, learned SPC, assisted by Ms.Resmi C. Senan, appeared for the first respondent. Both the appellant and the second respondent also filed written submissions.

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12. Ms.Vindhya Mani commenced her submissions by stating that the impugned order dealt with both the Controller's objections and the objections of the opponent. After pointing out that the Controller rejected the patent application *inter alia* by invoking the last limb of Section 3(d) of the Patents Act, which excludes from the definition of an invention “the mere use of a known process”, learned counsel submitted that, in order to reject the patent application on the said ground, reasons should be recorded for concluding that the appellant made a claim in respect of a known process. In the absence of any discussion as to how the appellant's process was known, she submitted that the conclusion that Section 3(d) is attracted cannot be sustained.

13. Learned counsel next dealt with the conclusion that the claimed invention is a mere admixture resulting only in the aggregation of the properties of the components thereof, and therefore within the scope of Section 3(e) of the Patents Act. After

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pointing out that such conclusion was drawn on the ground that the appellant had not provided comparative data of the pre-lyophilized formulation and reconstituted formulation, learned counsel submitted that the standard adopted by the first respondent was erroneous. According to learned counsel, in order to surmount the exclusion under Section 3(e), the appellant is required to establish that the composition is greater than the sum of its parts. She further submitted that Tables 40 and 41 of the complete specification clearly disclose the synergy between the active ingredient, i.e. the peptibody, and the excipients. With particular reference to Table 41, she pointed out that the stability data of the composition varied considerably depending on whether tween-20 / polysorbate was included or excluded therefrom. Learned counsel contended that this clearly establishes the synergy between the ingredients of the composition.

14. As regards sufficiency, learned counsel submitted that the Patents Act requires the patent applicant to disclose the best method of performing the invention, which is known to the applicant, and not

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to provide experimental data for every exemplification or embodiment thereof. In this regard, she pointed out that the appellant had satisfied disclosure requirements in relation to SEQ ID 1017 and contended that it is unnecessary to do so for all 52 mimetic peptibodies.

15. With regard to the conclusions on alleged lack of inventive step, learned counsel referred to the decision of the European Patent Office (EPO) in respect of the claimed invention, and pointed out that the EPO acknowledged that a lyophilization formulation is peptibody-specific. By referring to the experimental data, learned counsel submitted that the said data is sufficient to establish that the claimed invention would not be obvious to a person skilled in the art (PSITA) on the basis of cited prior arts. Out of the cited prior arts, learned counsel submitted that prior arts D1, D2 and D4 pertain to the appellant's inventions. According to her, the said prior arts do not disclose a lyophilized formulation of a peptibody. As regards prior art D3, she submitted that it discloses excipients, but contains no

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reference to a peptibody. As regards prior art D5, she submitted that the active ingredient therein is a particular protein called Interleukin-12 (IL-12), which is a heterodimeric cytokine, and not a peptibody, i.e a substance formed by the fusion of a peptide and the Fc domain of an antibody. Since lyophilization formulation is peptibody-specific, she contended that PSITA would not combine the excipients in prior art D5 with the peptibody of prior art D4 to arrive at the claimed invention.

16. In support of these contentions, learned counsel referred to and relied upon the following judgments:

(i) *Nippon Steel Corporation v. The Controller General of Patents, Designs and Trade Marks and another in C.A.(Comm. IPD-PAT) 323 of 2022, order dated 29.08.2024,* for the proposition that the known process should be identified.

(ii) *Dhama Innovations Private Limited v. The Assistant Controller of Patents and Designs in CMA(PT) No.12 of 2024, dated 19.07.2024,* for the proposition that the dissection of a combination

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into its constituent elements and the examination of each element in order to see whether its use was obvious or not is impermissible as it tends to obscure the fact that the invention claimed is in respect of a combination.

(iii) *Net MoneyIN, Inc, v. Verisign Inc., United States Court of Appeals for the Federal Circuit 2007-1565*, at pages 15 and 19 thereof.

(iv) *In Re: Stepan Company*, Court of Appeals for the Federal Circuit, MANU/USFD/0346/2017

(v) *Steel Strips Wheels Limited v. Wheels India Limited and another*, *2025:MHC:922*.

(vi) *Caleb Suresh Motupalli v. Controller of Patents, 2025:MHC:293*.

(vii) Decision of the Enlarged Board of Appeal dated 18.06.2025 in *Yunnan Tobacco International Co. Ltd. v. Philip Morris Products S.A, G 0001/24*.

(viii) Decision of the European Technical Board of Appeal dated 31.01.2024 in *Teva Pharmaceutical Industries Ltd v. United States*

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of America, rep. By Secretary, Department of Health and Human Services, T 2395/22-3.3.02, particularly, paragraphs 12.1.1 and 17.

(viii) *Ajantha Pharma Limited v. Allergan Inc. ORA/21/2011/PT/KOL.*

(ix) *General Electric Company's Applications [1964] 81 RPC 413.*

17. Mr. Majumdar, learned counsel, made submissions in response. He opened his arguments by pointing out that the claimed invention consists of one active ingredient and four excipients. While the original claims extended to five formulae, he submitted that the rejected claims were confined to one active ingredient (Formula-V). He first dealt with the opposition on the ground that the claimed invention did not exhibit synergy between the ingredients thereof. On this issue, he referred to paragraph 7.4 of the opposition and paragraph 64 of the written submissions to contend that prior art teaches compositions exhibiting similar stability. With further reference to paragraph [0084] of the complete specification, he

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submitted that it is evident from Table A therein that the use of the excipients of the claimed invention to lyophilize a protein formulation was known in the prior art.

18. As regards lack of inventive step, by referring to prior art D4, he submitted that it deals with the same peptibody. With specific reference to page 789, column 6 of the rejoinder volume read with pages 792 and 794 thereof, learned counsel submitted that SEQ ID 1017, which finds place therein, is the same as Formula V. After further submitting that the complete specification of D4 covers composition claims, he submitted that it also discloses lyophilization.

19. According to learned counsel, all the excipients used in the claimed invention are disclosed in prior art D5 in relation to the preparation of a lyophilized composition of a protein. He rebutted the contention that a peptibody is different from a protein by pointing out that the words 'protein' and 'peptibody' are used interchangeably in the complete specification of the claimed invention. By referring to

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line 21 of page 730 and lines 23 to 35 of page 731 of the rejoinder volume, learned counsel submitted that prior art D3 also discloses lyophilization. By revisiting Table A of the complete specification, learned counsel submitted that it contains the catalogue or menu of excipients. Out of the types of excipients, as regards buffering agents, by referring to paragraph [0098] of the complete specification of the claimed invention, learned counsel submitted that the buffering agents mentioned therein include succinate and histidine. By comparing the said paragraph with prior art D5 at page 826 of the rejoinder volume, he pointed out that the use of both succinate and histidine as buffering agents is disclosed in D5. Likewise, as regards stabilizers, learned counsel submits that D5 discloses the use of sucrose of 0.5 to about 2% concentration, most preferably about 2%. He points out that this is the exact concentration mentioned in the claims of the claimed invention.

20. He then pointed out that D5 discloses the use of mannitol, as a bulking agent, at a concentration of about 3 to 5%, most

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preferably about 4.15%. By turning to the claimed invention, learned counsel submitted that it provides for mannitol concentration of 4%, which is not materially different from 4.15%. In this connection, by referring to Tables 40 and 41, learned counsel submitted that the experimental data show that variations in the concentration of mannitol do not have any effect on stability. With regard to the use of surfactants, learned counsel submitted that D5 discloses the use of polysorbate selected from a group consisting of tween-20 or tween-80, most preferably tween-20. As regards concentration also, he submitted that D5 discloses the range of 0.001-0.1%, preferably 0.001-0.1%, most preferably about 0.02%. Although the claimed invention specifies tween-20 concentration of 0.004%, with reference to example – 7 of the complete specification of the claimed invention, and, in particular, Tables 40 and 41 thereof, learned counsel submitted that no reasoning has been provided for choosing 0.004% tween-20 except saying that 0.002% to 0.006% is sufficient. Therefore, he submitted that the claimed invention would be obvious to PSITA starting with D4 and combining D4 and D5.

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21. In support of these contentions, learned counsel referred to and relied upon the following judgments:

(i) *British Celanese Ltd. v. Courtaulds Ltd. [1935] 52 RPC 171* for the proposition that in the absence of interrelated working of known integers, there is no synergy.

(ii) *Bishwanath Prasad Radhey Shyam v. Hindustan Metal Industries, (1979) 2 SCC 511*, for the proposition that mere workshop improvement does not meet the test of invention or inventive step.

(iii) *Rhodia Operations v. The Assistant Controller of Patents and Designs, 2024: MHC:449 (Rhodia Operations)*, particularly paragraphs 45 and 49 thereof.

(iv) *Fresenius Kabi Oncology Limited v. Glaxo Group Limited and Another, 2013 SCC OnLine IPAB 121*, particularly paragraphs 58 and 60 thereof.

(v) *Indian Institute of Technology v. The Controller of Patents and Designs and Others, 2024:MHC:2264*, particularly paragraphs

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29 and 35 thereof.

(vi) *Novozymes v. Asst. Controller of Patents & Designs 2023 MHC 4261.*

(vii) *Sankalp Rehabilitation Trust v. F. Hoffman-LA Roche AG 2012 SCC OnLine IPAB 167.*

(viii) *Mahesh Gupta v. Asst. Controller of Patents and Designs 2024 SCC OnLine Del 4000.*

(ix) *Exxonmobil oil corporation v. Treofan Germany GmbH & Co. KG T 0532/00 – 3.3.9*

(x) *In re Aller et al., 220 F.2d 454*

22. The first respondent submitted that the active ingredient in the claimed invention is a known peptibody, and that lyophilization is also a known technique for increasing the shelf-life of protein formulations. The first respondent submitted further that all the excipients of the claimed invention are present in the cited prior arts, which also relate to protein formulations. Therefore, it was submitted that the method claim of the claimed invention (claim 9) is mere use

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of a known process and falls within the scope of Section 3(d) of the Patents Act. In the absence of comparative data with regard to pre-lyophilization and post-lyophilization stability, it was submitted that synergy has not been established. Consequently, it was contended that the exclusion under Section 3(e) applies.

23. As regards the lack of inventive step, the first respondent contended that the types of excipients used in the claimed invention are commonly used in protein compositions. Regarding the use of stabilizers, it was submitted that the use of sucrose and mannitol is common when the active ingredient is a protein. Similarly, it was submitted that polysorbate is very commonly used as a surfactant when the active ingredient is a protein. The next contention was that Tables 40 and 41 of example 7 are inadequate to establish either inventive step or synergy because the concentration of protein varies. As regards sufficiency, by pointing out that Formula V of the claimed invention consists of 52 peptide mimetics and that data was provided only in respect of SEQ ID 1017, it was contended that the claimed

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invention does not meet the requirements of Section 10 of the Patents Act.

24. By way of rejoinder, Ms.Vindhya Mani submitted the following: she pointed out that prior arts D5 and D2 deal with proteins and not peptibodies. She further submitted that the submissions of the first respondent were contradictory. On the one hand, she submitted that the first respondent contended that there are 52 peptide mimetics and that the claimed invention suffered from lack of enablement because experimental data was not provided for all 52 peptide mimetics. On the other, she pointed out that it was submitted that the claimed invention is obvious because there is a limited choice of excipients for a protein/peptibody. By referring to the EPO order in respect of the claimed invention, learned counsel pointed out that the concentration of excipients varies from molecule to molecule and that this is evident by comparing paragraph 3.5.1 with paragraph 3.5.2 of the EPO order.

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25. As regards the objection on the basis of Section 3(e), by referring to Tables 40 and 41, she submitted that the appellant has demonstrated the synergy between the active ingredient and excipients, particularly tween-20, and that it is unnecessary to provide data with regard to pre and post lyophilization stability. For purposes of Section 10(4)(d) of the Patents Act, learned counsel submitted that it is not necessary to exemplify all 52 peptide mimetics. After pointing out that prior art D5 deals with a particular protein called IL-12, which is a heterodimeric cytokine, she referred to the definition of peptibody at page 23 of the rejoinder volume to emphasize the differences between a protein and a peptibody.

26. Without prejudice to this contention, she pointed out that the concentration of mannitol in D5 is preferably 4.15% and that PSITA would have no motivation to change this to 4%. With regard to tween, she pointed out that the concentration in D5 is 0.02% as opposed to 0.004% in the claimed invention. As regards the pH, she submitted that it was 5.2% to 7.4% in D5 as opposed to 5% in the

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claimed invention. By referring to the decision of the EPO dated 31.01.2024, particularly paragraphs 12.1.1, 17.2, 17.2.6, 17.3.9 and 17.3.11 thereof, she submitted that the EPO concluded that the choice of concentration of D mannitol, which was the only excipient in that case, in a lyophilization process was considered as inventive. Thus, she submitted that none of the prior arts teach lyophilization of peptibodies. Given the range of permutations and combinations involved in combining the peptibody with specific excipients of specific concentrations from and out of four types of excipients, she submitted that the claimed invention would not be obvious to PSITA.

Discussion, analysis and conclusions:

27. At the outset, it is pertinent to state that the original set of claims covered therapeutic peptibodies comprising the structures in Formulae-I-V of original claims 1 to 5. In the final rejected claims, Formulae I-IV were given up and only Formula-V was retained by the appellant. The rejected claims comprise a set of 13 claims. Independent claim 1(composition claim), dependent claim 8 and

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independent claim 9 (method claim) thereof are set out below:

1. A lyophilized therapeutic peptibody composition comprising a buffer, a bulking agent, a stabilizing agent, and a surfactant;
wherein said pH buffering agent is 10 mM histidine and wherein the pH is 5.0;
wherein said bulking agent is 4% w/v mannitol;
wherein said stabilizing agent is 2% w/v sucrose;
wherein said surfactant is 0.004% w/v polysorbate-20;
wherein said therapeutic peptibody comprises a structure set out in Formula V

Formula V:$[F^1\text{-}(L^1)_e\text{-}P^1\text{-}(L^2)_f\text{-}P^2]\text{-}(L^1)_c\text{-}WSP_d$

wherein:
F^1 *is an Fc domain attached at the N-terminus of*
$\text{-}L^1\text{-}P^1\text{-}L^2\text{-}P^2$;
P^1 *and* P^2 *are each independently selected from Table 6;*
L^1 *and* L^2 *are each independently linkers;*
e and d are each 0; and

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e and f are each independently 0 or 1.

8. The composition of any one of claims 1-7 wherein the peptibody comprises SEQ ID No:1017.

9. A method for making a lyophilized therapeutic peptibody comprising the steps of:

a) preparing a solution of a buffer, a bulking agent, a stabilizing agent, and a surfactant;

wherein said pH buffering agent is 10mM histidine and pH is 5.0;

wherein said bulking agent is 4% w/v mannitol;

wherein said stabilizing agent is 2% w/v sucrose; and

wherein said surfactant is 0.004% w/v polysorbate-20; and

b) lyophilizing said therapeutic peptibody solution;

wherein said therapeutic peptibody comprises a structure set out in Formula V

***Formula V**: $[F^1\text{-}(L^1)_e\text{-}P^1\text{-}(L^2)_f\text{-}(L^1)_e\text{-}WSP_d$*

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wherein:

F^1 is an Fc domain attached at the N-terminus of -L'-P'-L^2-P^2;

P^1 and P^2 are each independently selected from Table 6;

L^1 and L^2 are each independently linkers;

c and d are each 0; and

e and f are each independently 0 or 1.

Against the backdrop of the above claims, I first consider the rejection under Section 3(d) of the Patents Act.

Rejection under Section 3(d)

28. With reference to independent claim 9, which is the method claim, it was held by the first respondent that the said claim is excluded under Section 3(d) of the Patents Act from patent protection. Section 3(d) is set out below:

> *"**3. What are not inventions.**- The following are not inventions within the meaning of this Act,-*
>
> *[(d) the mere discovery of a new form of a known substance which does not result in the enhancement of the known efficacy of*

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that substance or the mere discovery of any new property or new use for a known substance ***or of the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant.*** (emphasis added)

Explanation.- For the purposes of this clause, salts, esters, ethers, polymorphs, metabolites, pure form, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substance shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy;]"

29. The first respondent concluded that independent claim 9 relates to the mere use of a known process. As is noticeable from the text of claim 9, it is in respect of a method for making a lyophilized therapeutic peptibody comprising the structure set out in Formula V. According to the first respondent, the peptibody comprising the structure set out in Formula V was disclosed in prior art D4 and that

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lyophilization is also a well known process. Therefore, it was concluded that the above mentioned claim is no more than the mere use of a known process. The relevant findings are as under:

> *"The applicant has argued that the controller has not raised an objection novelty in FER or in Hearing notice. Originally filed application lacks clarity, broad scope and has not met the unity of invention. In that scenario it is difficult to determine the novelty, but documents has cited for inventive step on the basis of lyophilized composition. With respect to FER the applicant refers to a specific Seq ID for P1 and P2 which have 100% similarity with Seq id 13 of D7. Formula 5 with 100% similar seq ID was disclosed in D7. The documents cited for the inventive step clearly explains the significance of D3 and D7. Moreover all the ingredients of the instant specification are also disclosed in D7. In this scenario, the instant method claims 9-12 can be considered as mere use of a known process and the objection is retained."*

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30. This was refuted by learned counsel for the appellant on the ground that none of the cited prior arts relate to the lyophilization of the therapeutic peptibody comprising the structure of Formula V. On examining the cited prior arts, I find that D4 does disclose a therapeutic peptibody of the structure of Formula V. At column 19 of D4, lyophilization is referred to in the following terms:

> *"…. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form."*

Although the use of excipients is also referred to in column 19 of D4 and ingredients like sucrose are referred to, the process of lyophilizing the therapeutic peptibody is not recited therein. D5 discloses a lyophilized composition of IL-12 by use of excipients, but it does not describe the method of lyophilizing the therapeutic peptibody of Formula V. In fact, D5 contains only composition claims and no method claims. I also find that independent claim 9 recites the use of specific excipients of specific excipient categories, such as buffering agent (at a specific pH), bulking agent, stabilizing agent and

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surfactant, at specific concentrations. Therefore, the process described in independent claim 9 cannot be characterized as the mere use of a known process. Consequently, the rejection under Section 3(d) of the Patents Act is not sustainable. I turn next to the rejection under Section 3(e) of the Patents Act.

Rejection under Section 3(e):

31. The second respondent contended and the first respondent concluded that the composition of the claimed invention does not demonstrate synergy and is therefore not entitled to protection by virtue of the exclusion under Section 3(e) of the Patents Act. In order to decide this issue, it is first necessary to extract Section 3(e):

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

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As is evident from the text of clause(e), a substance obtained by mere admixture resulting in the aggregation of the properties of the components thereof is excluded from patent protection. In order to surmount the Section 3(e) barrier, it is, consequently, necessary for the patent applicant to establish that the composition exhibits synergy as between the ingredients thereof, and that the composition is more than the sum of its parts.

32. In the impugned order, it was recorded by the first respondent that the appellant failed to provide a comparison between the pre-lyophilized formulation and the reconstituted formulation. In the absence of such data, it was held that the exclusion under Section 3(e) is attracted. The findings, in relevant part, are as under:

> "*Regarding Tables 40 and 41 which indicates the formulation studies, elucidate data on the stability of the samples by optimization with different excipients and concentrations. The data on stability with different concentration of sucrose and mannitol with and without Tween at a*

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protein concentration of 0.3mg/ml was demonstrated in Table 41 for time 0, 4 months and 1 year.

Table 40 demonstrated a protein of 0.5 mg/ml with different concentrations of sucrose and mannitol.

There is no data regarding pre-lyophilization and reconstituted formulation to compare the improved technical effect. Other than an optimization, no technical advancement has been clearly stated in the specification. Hence, the objection u/s. 3(e) is retained for the latest amended claims 1-8."

Submissions on the same lines were advanced in this appeal on behalf of the first respondent. In response to this contention, learned counsel for the appellant submitted that Section 3(e) does not require the production of pre-lyophilization and post-lyophilization data. According to learned counsel, it is sufficient if the appellant establishes that the composition is more than the sum of its parts.

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33. Table 39 of the complete specification provides data relating to stability when the therapeutic peptibody is buffered at pH5 with tween-20 by varying the percentage of the stabilizing agent/lyoprotectant, sucrose, and the stabilizing/bulking agent, mannitol. Chemical degradation was monitored in the experiment by cation-exchange chromatography and reversed-phase high performance liquid chromatography (HPLC) at the elevated temperature of 37°C. The results show that chemical degradation is much higher at 18 weeks if the concentration of sucrose is below 1.5%. The results also support the conclusion that it is insufficient to combine a low sucrose concentration with high mannitol concentration. In effect, the data in Table 39 supports the conclusion that sucrose lends stability to the API.

34. In Tables 40 and 41 of the complete specification, the appellant has provided data with regard to the measured percentage of aggregation of the composition. In Table 40, the therapeutic peptibody of 0.5 mg/mL has been lyophilized with 10 mM histidine

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(buffering agent), a stabilizing and bulking agent. Except in one experiment, the polysorbate (tween-20)/surfactant was not added. Where tween-20 was added, it was found that the percentage of aggregation after three months and 11 months was less than 0.1%. In all other cases, the measured percentage of aggregation was much higher. Where tween-20 was not used, wherever the sucrose concentration was low (below 2%), even where the mannitol concentration was high, the results show higher aggregation. Similarly, in Table 41, 0.3 mg/mL of the therapeutic peptibody was lyophilized by maintaining pH at 5. As in the case of Table 40, whenever tween-20 was added, the measured percentage of aggregation was much lower and, on the contrary, whenever tween-20 was not added, the measured percentage of aggregation was higher.

35. As is evident from the findings, the first reason for upholding the objection under Section 3(e) is that different protein concentrations were used in Tables 40 and 41. Both Tables 40 and 41

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were intended to demonstrate the decrease in aggregation whenever tween-20 was used. This was shown with regard to two different concentrations of the therapeutic peptibody. Therefore, the rejection on the ground that experiments were conducted at different protein concentrations is not germane given the object of the experimental data in Tables 40 and 41.

36. The other reason mentioned in the impugned order with regard to Section 3(e) is that there is no pre-lyophilization and post-lyophilization/reconstituted formulation data. The object of the claimed invention is to increase the stability of the therapeutic peptibody by the process of lyophilization. Unlike in the case of prior art D3, the object is not to increase the protein concentration of the composition by lyophilization. Because the object of prior art D3 was to increase the protein concentration by lyophilization, pre-lyophilization and post-lyophilization data was provided in D3. For purposes of establishing synergy, it is sufficient if the appellant demonstrates interaction between the ingredients and, consequently,

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that the composition is more than the sum of its parts. Data relating to pre-lyophilization and post-lyophilization is not relevant for purpose of Section 3(e) and the conclusion that the claimed invention is excluded from protection under Section 3(e) on that account is rejected is untenable.

37. The conclusion that follows from this discussion is that Tables 39 to 41 of the complete specification of the claimed invention contain evidence of synergy between the ingredients of the claimed invention. In fact, as discussed above, Table 39 discloses the synergy from using at least a threshold concentration of the stabilizing agent/lyoprotectant, sucrose, and Tables 40 and 41 disclose the anti-aggregation benefit by using the specified concentration of tween-20. Therefore, the rejection of the claimed invention by relying on Section 3(e) cannot be countenanced.

Rejection on the basis of lack of inventive step:

38. In the impugned order, the claimed invention was rejected

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on the ground of lack of inventive step by also upholding the objection of the second respondent in that regard. The relevant findings are as under:

> *"Lyophilization is one the known technique in art for the stabilization and improved shelf life of proteins/antibodies. Buffer, bulking agent, stabilizing agent and surfactant are the common excipients in the lyophilization process. The choice of the excipients and the optimization will be determined by route of administration, delivery and desired dosage.*
>
> *Compounds of Formula V are known in the art. It is evident from D2 about the increased half-life by the addition of Fc domains. D2 discloses formula V i.e. a peptibody with an identical formula along with a pharmaceutical composition, D4 discloses SEQ ID 34 is the same as SEQ ID.1017 of the present invention, D7 was discloses Formula V and SEQ ID 13 of D7 is 100% similar with SEQ ID 459.*

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Even though D1 did not disclose Formula V, it disclosed about peptibodies with Fc domains, particularly of Formula 1 of the originally filed instant application. The document D1 talks about lyophilization, reconstitution and kit, which is already known in the prior art and the significance of the same for the route of administration, delivery and desired dosage. The technical advance or economic significance or both in the invention disclosed in the instant application as compared to the D1 is obvious to person skilled in the art since it discloses routine modifications which are known to person skilled in the art.

Method of lyophilization, reconstitution and kit was disclosed in D1, D3, D5 and D6. It would be obvious to person skilled in the art to lyophilize a known peptibody which was disclosed in the prior art for the improved shelf life. The excipients and the range of excipients are already disclosed in the prior art documents. The desired effect claimed by the applicant can be obtained by

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optimization, which cannot be considered as a technical feature for inventiveness as it would have been obvious to one ordinary skilled in the art. There is no data regarding pre-lyophilization and reconstituted formulation to compare the improved technical effect/storage stability. The applicant has provided data for optimization of various excipients and concentrations. The technical advance as compared to the existing knowledge was not established in the specification. Other than an optimization, no technical advancement has been clearly stated in the specification. Hence inventive cannot be acknowledged for the instant invention and objection u/s 25(1)(e) stands valid."

Prior arts

Six prior arts were cited in the FER. Out of these, the sixth prior art was non-patent literature. In the first hearing notice dated 27 April 2016, D3 and an additional prior art labelled as D7, WO 2000024782, were cited. By reply dated 24 June 2016, the appellant contended that D7 is directed at the fusion of the Fc domain of a

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peptide to increase the *in vivo* half life and that it does not teach the use of specific excipients. Later, in the pre-grant opposition, the second respondent cited five prior arts, which were labelled therein as prior arts D1-D5. Only these five prior arts were placed on record in this appeal. Hence, in order to decide whether this ground of rejection is sustainable, a discussion of these cited prior arts is warranted. This exercise should be carried out by donning the mantle of a PSITA. The relevant art in this case is the formulation of biologics, and PSITA would be a formulation scientist. While knowledge and skill would be attributed to the notional PSITA, excellent/outstanding skill and ingenuity would not be attributed (see *Rhodia Operations).*

39. Prior art D1 relates to patent literature titled “METHODS OF TREATMENT USING SPECIFIC BINDING AGENTS OF HUMAN ANGIOPOIETIN-2”, and the patentee is the appellant herein. D1 is directed at peptides, including peptides fused to Fc domains and thereby forming peptibodies. The accepted claims of D1 covered the

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peptide of specific SEQ IDs set out in the claims. The agreed position is that D1 does not disclose the active ingredient, i.e. therapeutic peptibody, of the claimed invention or deal with lyophilization.

40. D2 is patent literature titled "MODIFIED PEPTIDES AS THERAPEUTIC AGENTS", and the patentee is the appellant herein. The object of D2 is clear from the summary of the invention. In such summary, it is stated that D2 concerns a process by which the *in vivo* half life of one or more biologically active peptides is increased by fusion with preferably the Fc domain of an antibody. Independent claim 1 of D2 is as under:

> *"1. Composition of matter claims A composition of matter of the formula*
>
> $(X^1)_a$-F^1 - $(X^2)_b$
>
> *and multimers thereof, wherein:*
>
> F^1 *is an Fc domain;*
>
> X^1 *and* X^2 *are each independently selected from* - $(L^1)_c$-P^1, - $(L^1)_c$-P^1- $(L^2)_d$– P^2, - $(L^1)_c$ – P^1 – $(L^2)_d$ – P^2 – $(L^3)_e$ – P^3, *and* – $(L^1)_c$ – P^1 – $(L^2)_d$ – P^2 – $(L^3)_e$ – P^3 – $(L^4)_f$– P^4
>
> P^1, P^2, P^3, *and* P^4 *are each independently*

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sequences of pharmacologically active peptides;

L^1, L^2, L^3, and L^4 are each independently linkers; and

a, b, c, d, e, and f are each independently 0 or 1, provided that at least one of a and b is 1."

As is evident from independent claim 1 of D2, D2 makes a monopoly claim over a process of combining sequences of pharmaceutically active peptides with the Fc domain of an antibody.

41. From the complete specification read with the claims of D1 and D2, the conclusion that emerges is that D1 does not disclose the active ingredient of the claimed invention and does not deal with or refer to lyophilization. While D2 deals with both erythropoietin (EPO) mimetic peptide sequences and TPO mimetic peptide sequences, D2 also does not deal with or refer to lyophilization.

42. D3 is patent literature relating to an invention titled

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"STABILE ISOTONIC LYOPHILIZED PROTEIN FORMULATION".

The problem that D3 set out to resolve is evident from the summary of the invention, wherein, in relevant part, it is stated as under:

> *"**Summary of the Invention***
>
> *This invention is based on the discovery that a stable lyophilized protein formulation can be prepared using a lyoprotectant (preferably a sugar such as sucrose or trehalose), which lyophilized formulation can be reconstituted to generate a stable reconstituted formulation having a protein concentration which is significantly higher (e.g. from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the protein concentration in the pre-lyophilized formulation. In particular, while the protein concentration in the pre-lyophilized formulation may be 5 mg/mL or less, the protein concentration in the reconstituted formulation is generally 50 mg/mL or more. Such high protein concentration in the*

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reconstituted formulation are considered to be particularly useful where the formulation is intended for subcutaneous administration."

43. Because of the above mentioned object and purpose of D3, D3 sets out the pre-lyophilized formulation and reconstituted formulation at Table 10 of the complete specification thereof. The object and purpose is further underscored by independent claim 1, which is as under:

> *"1. A stable isotonic reconstituted formulation comprising a protein in an amount of at least about 50 mg/mL and a diluent, which reconstituted formulation has been prepared from a lyophilized mixure of a protein and a lyoprotectant, wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixure before lyophilization."*

As is evident from the above, D3 makes a claim in respect of a

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reconstituted formulation comprising a protein and a diluent prepared from a lyophilized mixture of a protein and a lyoprotectant, wherein the protein concentration in the reconstituted formulation is about 2-40 times greater than the protein concentration in the mixture before lyophilization. For purposes of lyophilization, the dependent claims of D3 provide for the use of sucrose or trechalose as the lyoprotectant, the use of histidine or succinate as the buffer and for the use of a surfactant. When read with Table 10 of D3, it appears that the surfactant is 0.04% of polysorbate -20.

44. Since D3 discloses both a formulation comprising protein and a lyoprotectant along with other excipients, it becomes necessary to discuss whether PSITA would be led to the claimed invention by D3. If PSITA were armed with the knowledge of D3, PSITA would be focused on increasing the protein concentration in a lyophilized protein formulation and not on undertaking lyophilization for purposes of enhancing the stability of the protein/peptide/peptibody. Except for specifying the deployment of a lyoprotectant, a buffer and

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a surfactant, the specific concentrations of the excipients are not provided in D3. Thus, especially in view of the problem being addressed by D3, I conclude that PSITA would not arrive at the claimed invention on the basis of D3.

45. D4 is patent literature titled "THROMBOPOIETIC COMPOUNDS", and the patentee is the appellant. As in the case of the claimed invention, the composition of D4 also deals with a TPO peptibody. It bears repetition that TPO plays a significant role in the production of platelets in the human body. The object of D4 is evident from the summary of D4, which, in relevant part, is as under:

"SUMMARY OF THE INVENTION

The present invention provides a group of compounds that are capable of binding to and triggering a transmembrane signal through, i.e., activating, the c-MP1 receptor, which is the same receptor that mediates the activity of endogenous thrombopoietin (TPO). Thus, the inventive compounds have thrombopoietic activity, i.e., the ability to

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stimulate, in vivo and in vitro, the production of platelets, and/or megakaryocytopoietic activity, i.e., the ability to stimulate in vivo and in vitro, the production of platelet precursors."

Therefore, D4 contains a list of inventive compounds that have thrombopoietic activity.

46. D4 recites as under with regard to a second embodiment of the invention:

"In a second embodiment of this invention, the compounds described above may further be fused to one or more Fc groups, either directly or through linker groups. In general, the formula of this second group of compounds is:

$(Fc)_m$-$(L_2)_q$ – TMP_1 – $(L_1)_n$ – TMP_2 – $(L_3)_r$ $(FC)_p$

wherein TMP_1 , TMP_2 *and n are each as described above; L1, L2 and L3 are linker groups which are each independently selected from the linker groups described*

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above, Fc is an Fc region of an immunoglobulin; m, p, q and r are each independently selected from the group consisting of 0 and 1, wherein at least one of m or p is 1, and further wherein if m is 0 then q is 0, and if p is 0, then r is 0; and physiologically acceptable salts thereof."

Learned counsel for the second respondent contended that the formula extracted above is Formula V of the claimed invention. In other words, his contention is that the therapeutic peptibody of the claimed invention was disclosed in D4. This contention is admitted by the appellant and is, in any event, evident on examining D4. This leads to the question whether PSITA would be led to the claimed invention by D4.

47. In order to buttress the contention that the claimed invention would be evident to PSITA from D4, learned counsel for the second respondent referred to the discussion and disclosures with regard to pharmaceutical compositions in the complete specification

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of D4. In particular, he relied on the following recitals in column 19 of D4:

> *"The pharmaceutical compositions optionally may include still other pharmaceutically acceptable liquid, semisolid, or solid diluents that serve as pharmaceutical vehicles, excipients, or media, including but are not limited to, polyoxyethylene sorbitan monolaurate, magnesium stearate, methyl- and propylhydroxybenzoate, starches, sucrose, dextrose, gum acacia, calcium phosphate, mineral oil, cocoa butter, and oil of theobroma. Such compositions may influence the physical state, stability, rate of in vivo release, and rate of in vivo clearance of the present proteins and derivatives. See, e.g. Remington's Pharmaceutical Sciences, 18th Ed.(1990, Mack Publishing Co., Easton, Pa.18042) pages 1435-1712 which are herein incorporated by reference. The compositions may be prepared in liquid form, or may be in dried powder, such as lyophilized form. Implantable sustained release formulations*

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are also contemplated, as are transdermal formulations."

48. The question that, therefore, arises is whether PSITA, when armed with D4, would be in a position to arrive at the claimed invention on the basis of the above disclosure relating to lyophilization in D4. It is noticeable that, while dealing with compositions, D4 refers in general to the use of excipients and mentions ingredients like sucrose, dextrose and calcium phosphate. It also draws reference to the preparation of the composition in dried powder such as lyophilized form. D4 does not provide any further information with regard to lyophilization or deal with categories of excipient, such as stabilizers, buffering agents, bulking agents and surfactants. D4 also does not deal with or specify the appropriate concentrations of the peptibody and excipients. Therefore, in my view, a non-inventive PSITA with knowledge of D4 cannot arrive at the claimed invention either solely on the basis of D4 or on the basis of D1 to D4. D5 remains to be considered.

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49. D5 is patent literature for an invention titled "FORMULATIONS FOR IL-12". IL-12, as indicated earlier, is an abbreviation for a protein called Interleukin-12. IL-12 is a heterodimeric cytokine, which induces the production of interferon by T cells in the human body. By resorting to recombinant DNA technology, IL-12 protein is being produced outside the human body. As is evident from the title of D5, it is directed at formulations for IL-12, including in lyophilized form.

50. The nature of D5 may be gleaned from the brief summary which is as under:

> *"BRIEF SUMMARY OF THE INVENTION*
>
> *One aspect of the present invention provides novel composition and methods for providing concentrated preparations of IL-12, useful as drug product. These compositions, either frozen, liquid, or lyophilized (preferably lyophilized) comprise: (a) a protein selected from the group consisting of IL-12, a biologically active fragment of IL-12, a subunit of IL-12,*

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and a multimer of a subunit of IL-12, (b) a polysorbate; (c) a cryoprotectant; (d) a bulking agent; and (e) a buffering agent which maintains the pH of said composition in the range of from about 4.5 to about 7.4.

Preferably, the cryoprotectant is selected from the group consisting of sucrose, maltose, lactose and combinations thereof. Preferably, the cryoprotectant comprises about 0.5 to about 5% of the composition. When sucrose is used, a preferred concentration is from about 0.5 to about 2%, most preferably about 2%. Preferably the bulking agent is selected from the group consisting of mannitol, glycine and combinations thereof. Preferably the bulking agent comprises about 1 to about 5% of the composition. When mannitol is used, a preferred concentration is from about 3 to 5%, most preferably about 4.15%. Combinations of sucrose/mannitol and sucrose/glycine are particularly preferred.

Preferably the polysorbate is selected from the group consisting of tween-20 and

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tween-80. Most preferably tween-20. In certain embodiments, the polysorbate is present at a concentration of about 0.001 to 0.1%, preferably at a concentration of about 0.001 to 0.1%., most preferably at a concentration of about 0.02% plurality of polysorbates may also be used.

In preferred embodiments, the buffering agent maintains the pH of said composition in the range of from about 5.2 to about 7.4, most preferably at about 5.6. Preferred buffering agents are selected from the group consisting of succinate, histidine, phosphate, Tris, and diethanolamine, with succinate (particularly the sodium and potassium salts thereof) being most preferred.

Preferably the protein is present at a concentration of about 1µg/ml to about 20 mg/ml, more preferably at about 1 to about 1000 µg/ml, most preferably at a concentration of about 5 to about 500 µg/ml.

Particularly preferred embodiments of the invention comprise about 5 to about 500

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µg/ml IL-12 , about 2% sucrose, about 4.15 % mannitol, about 10 mM sodium succinate, and about 0.02% tween -20, and having a pH of about 5.6."

51. In order to consider whether the PSITA would make a mosaic of prior arts D4 and D5 to arrive at the claimed invention, it is also necessary to set out the relevant claims of D5. Independent claim 1 and dependent claims 3, 5, 7, 9 and 11 are as under:

"1. A composition comprising: (a) a protein selected from the group consisting of IL-12, a biologically active fragment of IL-12, a subunit of IL-12, and a multimer of a subunit of IL-12; (b) a polysorbate; (c) a cryoprotectant; (d) a bulking agent; and (e) a buffering agent which maintains the pH of said composition in the range of from about 4.5 to about 7.4.

3. The composition of claim 2, wherein said cryoprotectant is sucrose.

5. The composition of claim 4, wherein said sucrose concentration is about 2%.

7. The composition of claim 6, wherein

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said bulking agent is mannitol.

9. The composition of claim 8, wherein said concentration is about 4.15%.

11. The composition of claim 10, wherein said polysorbate is tween-20.

52. Both learned counsel for the first and second respondents contended that D5 discloses the use of sucrose as a cryoprotectant and even specifies about 2% concentration. Likewise, it was submitted that the use of mannitol at the concentration of about 4.15% as the bulking agent and the use of tween-20 as the surfactant was disclosed. Given that PSITA is presumed to have knowledge of Formula V from D4, they contended that PSITA would turn to D5 to prepare a lyophilized formulation of the therapeutic peptibody of D4. Because D5 discloses all the excipients of the claimed invention, including by indicating substantially similar concentrations of such excipients, they contended that the claimed invention would be evident if a mosaic of D4 and D5 were made.

53. The process of lyophilization is well known and the

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appellant does not claim a monopoly in respect thereof. In fact, it was submitted on behalf of the first respondent that lyophilization is resorted to even while making instant coffee, and this contention was accepted without demur by the appellant. Even as between different proteins, it was submitted by the appellant that the choice of and concentrations of excipients would be required to be tailored based on the specific protein/active ingredient. The first respondent admitted that the choice of excipients while undertaking lyophilization depends on the active ingredient and on the mode of drug delivery/administration, but contended that it would be broadly the same while lyophilizing proteins. Learned counsel for the second respondent echoed and endorsed this contention. This aspect is vital for the adjudication of this dispute.

Scientific literature on excipients in lyophilization

54. Scientific literature on the selection of excipients for lyophilization would throw light on the issue outlined in the preceding paragraph. Given the dates of publication, none of the

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articles discussed in this and the succeeding paragraphs qualify as prior art in relation to the claimed invention. In the context of proteins, in the article titled "Excipient Selection for Protein Stabilization", authored by Cynthia A. Challener, Pharmaceutical Technology (2015, Issue 3, pp 35-39), the author states as under:

> *"Because every protein is different and reacts differently with different types of excipients, the selection of the proper excipients for a given formulation is a complex and challenging task. Some excipients may be effective in one formulation and cause protein degradation and aggregation in another."*

This article contains a discussion on the types of stabilizing agent, and states that factors to be taken into account to choose the excipients include the complex physical and chemical degradation behaviour of proteins, and the potential multi-functional influences that each excipient can have on the biologic. Noting that the formulation scientist must possess a thorough knowledge of optimization of physical and chemical stability of the API for

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rationally choosing the specific excipients and attaining optimal conditions for stability, the article concludes that excipient selection is a challenging task involving empirically strenuous efforts and resources.

55. In an article titled *"Excipient Use in Parenteral and Lyophilized Formulation Development"*, Open Science Journal of Pharmacy and Pharmacology (2015, Vol 3(3), pp 19-27), Yasir Mehmood and Umer Farooq list 10 bulking agents and 5 buffering agents used in lyophilization along with their critical process temperatures i.e. temperature above which the lyophilized product loses macroscopic structure and collapses during freeze-drying. The bulking agents include sucrose, lactose, trehalose, mannitol, sorbitol, glucose, rafinose, glycine, histidine, polyvinyl pyrollidone (K40) and the buffering agents include sodium citrate, sodium phosphate, Tris base-65, Tris acetate and Tris Hcl-65. Amongst the buffering agents, they cite acetate, citrate, tartarate, phosphate, triethanolamine as commonly used buffers in parenteral formulations. Further, it is

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stated that while selecting excipients for parenteral products, factors such as influence of excipients on the overall quality, stability, and effectiveness of the drug, compatibility of excipients with the drug, packaging system and manufacturing process should be borne in mind.

56. In an article titled "*Comprehensive Scientific Survey of Excipients Used in Currently Marketed, Therapeutic Biological Drug Products"* authored by V.Ashutosh Rao *et al* and published by the National Center for Biotechnology Information, a Division of the National Library of Health, 665 formulations, including 395 formulations deploying unique excipients, and supporting 211 therapeutic proteins as of June 2020 were studied. The list of biotechnology derived drug products approved or licensed by the Center for Drug Evaluation and Research (CDER) was used for evaluation. Based on the Handbook of Pharmaceutical Excipients, the excipients used in these formulations were classified as anti-adhesive agents, anti-microbial agents, buffering agents, pH adjusting agents,

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lyoprotectants, stabilizers, surfactants, tonicity agents, etc. Out of these categories, buffering agents, pH adjusting agents, lyoprotectants, stabilizers and surfactants are important for the adjudication of this case.

57. About 16 buffering agents are listed in the above mentioned article and the list includes acetate, histidine, lysine, alanine, arginine and succinic acid. The 6 lyoprotectants listed therein are: dextran 40, glycine, lactose, mannitol, sucrose and trehalose. In addition, three stabilizers, namely, albumin human, protamine sulphate and zinc are mentioned. As regards surfactants, palmitic acid, poloxamer 188, polysorbate 20, polysorbate 80 sodium lauryl sulphate, tripalmitin and colfosceril palmitate are specified. Biologics were classified therein into about eight categories, including antibody conjugates, cytokine and growth factors, enzyme, monoclonal antibody and recombinant fusion protein and the average prevalence of different categories of excipients was examined. The results disclose that about 84.63% contain a buffering agent, 56.17% contain a surfactant and

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52.39% contain a lyoprotectant. Among the specific excipients, sodium phosphate (a buffering agent) was found in 39.04% of the 397 unique formulations and polysorbate 80 was found in 32.49% of such formulations.

Conclusions on inventive step

58. Because the use of a peptibody as a biologic is not widespread, the categories of biologics in the above mentioned articles do not specifically include peptibodies. Nonetheless, as regards the use of specific categories of excipients, it appears that buffering agents, surfactants and lyoprotectants are most commonly used. Therefore, in my view, it would be obvious to a formulation scientist looking to lyophilize the peptibody of D4 to consider using a buffering agent, surfactant and lyoprotectant. In order to provide bulk and maintain the morphology of the lyophilized cake, it would also be obvious to use a bulking agent.

59. Whether it would be obvious to PSITA to select the specific

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excipients of the claimed invention in the specific indicated concentration under each category warrants careful consideration. Beginning this exercise with the stabilizer/lyoprotectant, the article discussed earlier refers to about 6 lyoprotectants and three stabilizers. Table A of the complete specification of the claimed invention refers generically to polyols, sugars and polymers. Turning next to the surfactant, the article discussed earlier referred to about 7 surfactants. The article also records that polysorbate 80 was the most widely used out of these surfactants in the 349 unique biologic formulations studied there. Table A of the complete specification discloses that "examples include polysorbate 20 and 80". With regard to buffering agents, the article disclosed about 16 excipients.

60. The conclusion that follows is that the same excipients are not used in the lyophilization of biologics or even in the lyophilization of proteins. Given the number of permutations and combinations, I further conclude that the composition and concentration of ingredients in the claimed invention would not be obvious unless

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there is teaching, motivation or suggestion that would lead PSITA to make a mosaic of D4 and D5 for such purpose. I turn to this aspect next.

61. D5 relates to formulations comprising a mimetic of a protein called IL-12. IL-12, as stated earlier, is a heterodimeric cytokine. A heterodimer protein is a protein complex formed by two different monomers/sub units. It is pertinent to state that IL-12 induces interferon production by T cells and plays a role in the treatment of cancer. By contrast, the active ingredient of the claimed invention is a peptide mimetic of a homodimeric protein (TPO) acting as a TPO-RA, which thereby enhances the production of platelets and is indicated in the treatment of ITP.

62. As is noticeable from the findings on lack of inventive step, the first respondent rejected the claimed invention largely on two grounds. The first ground being that lyophilization is a known technique in the stabilization of protein and that buffers, bulking

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agents, stabilizing agents and surfactants are common excipients for lyophilization. The second reason being that the compound of Formula V is disclosed in D2 and D4 and that the excipients were disclosed in D5. While the settled legal position is that a mosaic may be made of prior arts in course of obviousness analysis, such mosaic cannot be made by resorting to hindsight analysis. Put differently, there should be teaching, suggestion or motivation in the prior art which would lead PSITA to the claimed invention.

63. Although Formula V was disclosed in prior art D4 and there is a general reference to a lyophilized form of the therapeutic peptibody, nothing further is disclosed therein regarding lyophilization of the therapeutic peptibody. D5 deals with the lyophilization of IL-12, which is a distinct family of protein. In the absence of any teaching, suggestion or motivation in D4, which would direct PSITA to D5, given the distinct nature of proteins, there is no rational basis to conclude that PSITA, without the benefit of

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hindsight, would combine the excipients and concentrations indicated in D5 while setting out to prepare a lyophilized formulation of the peptibody of D4. Therefore, in my view, starting from D4, PSITA would look for patent or non-patent literature relating to the lyophilization of TPO-RA peptibodies or at least the lyophilization of TPO-RA peptides. The said process would not have led PSITA to make a mosaic of D4 and D5 so as to arrive at the claimed invention.

Rejection on the ground of lack of sufficiency:

64. With regard to alleged lack of sufficiency of disclosure, the first respondent contended that pre-lyophilization and post-lyophilization data was not provided. I recorded a finding earlier that such data was not required to be provided for present purposes. It was also submitted on behalf of the first respondent that Formula – V of the claimed invention consists of 52 peptide mimetics and that the appellant only provided experimental data relating to a Fc-TMP peptibody corresponding to a dimeric form of SEQ ID No.1017. In response to this contention, after pointing out that the first

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respondent has advanced incompatible and contradictory submissions, it was submitted by the appellant that all 52 mimetic peptides of the claimed invention belong to the same family. Therefore, it was contended that experimental data for SEQ ID No.1017 serves the purpose.

65. Sub-section (4) of Section 10 of the Patents Act mandates that every complete specification shall fully and particularly describe the invention and its operation or use, including the best method of performing the invention, as known to the applicant, and in respect of which the applicant is entitled to claim protection. Example 7 is contained in paragraphs [00255] to [00261] of the complete specification. The experimental data discussed therein is set out in Tables 39 to 41 and paragraphs [00262] to [00273].

66. Independent claims 1 and 9 of the rejected claims set out Formula V. Formula V, in turn, includes the elements P^1 and P^2, which cover all the 52 TPO mimetic peptide sequences set out in

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Table 6 of the complete specification. Out of these, SEQ.ID No.459 is the first. The amino acids in the said sequence with the corresponding single letter abbreviations are: Isoleucine(I), Glutamic acid(E), Glycine(G), Proline(P), Threonine(T), Leucine(L), Arginine(R), Glutamine(Q), Trytophan(W), Leucine, Alanine(A), Alanine, Arginine and Alanine. This sequence is expressed therein as IEGPTLRQWLAARA. In effect, this is a specific 14 amino acid sequence.

67. Peptibodies with peptides with the above mentioned amino acid sequence are contained in paragraph [00167] of the complete specification as SEQ ID Nos.1012, 1013, 1014, 1015, 1016 and 1017. To that extent, the peptibody mimetics have peptides with a common amino acid sequence and have been duly enabled, including by way of the experimental data in Example 7. As regards the remaining 51 mimetic peptide sequences in Table 6, although they relate to TPO mimetic peptide sequences, the sequences vary considerably. As between amino acids, the side chain (R chain) varies resulting in

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variation in molecular weight and structure. Amino acids fall broadly into six categories, namely, hydrophobic-aliphatic, hydrophobic-aromatic, polar neutral, acidic, basic and unique. Amino acid substitutions in a peptide sequence could have effects on structure and function depending on the nature of substitution. In the absence of guidance in the complete specification, given the varying characteristics of amino acid sequences and the complexities of arriving at a lyophilized peptibody formulation, in my view, the experimental data and disclosures in the complete specification are not sufficient to enable a PSITA of average skill and knowledge in India to carry out the process of preparing the composition of independent claim 1 by adopting the method of independent claim 9 in respect of the remaining 51 peptide mimetics in Table 6. Therefore, I conclude that the requirements of Section 10 of the Patents Act are only partly satisfied. As a corollary, it is necessary to curtail the width of the monopoly claim in independent claims 1 and 9.

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68. For reasons discussed above, subject to independent claims 1 and 9 being modified in the manner set out below, I conclude that the claimed invention satisfies all requirements of Section 2(1)(j), including Section 2(1)(ja), and Section 10 of the Patents Act. I further conclude that the claimed invention is not excluded from protection under Section 3(d) or 3(e). Therefore, the impugned order dated 31.03.2023 is set aside, the appeal is allowed without any order as to costs and it is directed that Patent Application No.5857/CHENP/2008 shall proceed to grant on the basis of the rejected claims subject to the following amendments to independent claims 1 and 9:

> *1. A lyophilized therapeutic peptibody composition comprising a buffer, a bulking agent, a stabilizing agent, and a surfactant;*
> *wherein said pH buffering agent is 10 mM histidine and wherein the pH is 5.0;*
> *wherein said bulking agent is 4% w/v mannitol;*
> *wherein said stabilizing agent is 2% w/v sucrose;*
> *wherein said surfactant is 0.004% w/v*

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polysorbate-20;

wherein said therapeutic peptibody comprises a structure set out in Formula V

***Formula V**:[F¹-(L¹)$_e$-P¹-(L²)$_f$-P²]-(L¹)$_c$-WSP$_d$*

wherein:

F¹ is an Fc domain attached at the N-terminus of

-L¹-P¹-L²-P²;

***P¹ and P² consist of peptides with the amino acid sequence of SEQ ID NO.459 of Table 6**;*

L¹ and L² are each independently linkers;

e and d are each 0; and

e and f are each independently 0 or 1.

9. A method for making a lyophilized therapeutic peptibody comprising the steps of:

a) preparing a solution of a buffer, a bulking agent, a stabilizing agent, and a surfactant;

wherein said pH buffering agent is 10mM histidine and pH is 5.0;

wherein said bulking agent is 4% w/v mannitol;

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wherein said stabilizing agent is 2% w/v sucrose; and

wherein said surfactant is 0.004% w/v polysorbate-20; and

b) lyophilizing said therapeutic peptibody solution;

wherein said therapeutic peptibody comprises a structure set out in Formula V

***Formula V**: $[F^1\text{-}(L^1)_e\text{-}P^1\text{-}(L^2)_f\text{-}(L^1)_c\text{-}WSP_d$*

wherein:

F^1 is an Fc domain attached at the N-terminus of -$L^{'}$-P'-L^2-P^2;

***P^1 and P^2 consist of peptides with the amino acid sequence of SEQ ID NO.459 of Table 6**;*

L^1 and L^2 are each independently linkers;

c and d are each 0; and

e and f are each independently 0 or 1.

(amendments emphasized in bold font)

22.08.2025

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

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