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OA/24/2020/PT/CHN

THURSDAY, THIS THE 31ST DAY OF DECEMBER, 2020

HON'BLE SHRI JUSTICE MANMOHAN SINGH — **CHAIRMAN**
HON'BLE DR. B.P. SINGH — **TECHNICAL MEMBER (PATENTS)**

THE UNIVERSITY OF BRITISH COLUMBIA
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BRITISH COLUMBIA V6T LZ3,
CANADA — APPELLANT

(Represented by: Ms. Nupur Maithani)

Versus

CONTROLLER OF PATENTS
ANNA SALAI, GUINDY INDUSTRIAL ESTATE,
SIDCO INDUSTRIAL ESTATE, GUINDY,
CHENNAI, TAMIL NADU 600032 — RESPONDENT

(Represented by - None)

ORDER

Hon'ble Shri Justice Manmohan Singh, Chairman

Hon'ble Dr. B.P. Singh, Technical Member (Patents)

1. The present appeal is filed under Section 117A of the Indian Patents Act, 1970, against the order dated 07/12/2016, passed by the Respondent, being the Assistant Controller of Patents & Designs, under Section 15 of the Indian Patents Act, refusing to grant the Appellant's Indian patent application no. 3588/CHENP/2010.

2. The present Invention as submitted by the appellant:

2.1 The invention claimed in the present application relates to monoclonal antibodies to the 14-3-3 η protein isoform. The monoclonal antibodies claimed demonstrate the following properties:

i. bind to the human 14-3-3 eta(η) isoform in its natural configuration; and

ii. exhibit selectivity for the human 14-3-3 η isoform over human 14-3-3 alpha (α), beta (β), delta (δ), epsilon (ε), gamma (γ), tau (τ) and zeta (ζ) isoforms.

3. The appellant submits the Experimental details provided in the present application as under:

3.1 Table 1 provides sequences details of 14-3-3 eta epitopes of SEQ ID NOs. 1-32. –Para [00184] on page 105 of the appeal

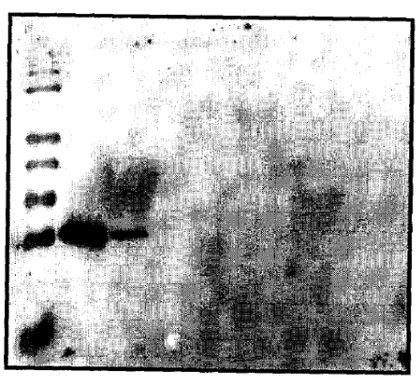
3.2 Example 1 on page 106 of the appeal discloses the production, selection and cloning of hybridomas for the production of monoclonal antibodies (mAbs) claimed in the present application.

Immunogens used for the production of mAbs

Immunogen	**Amino Acid Sequence**	**Similar Immunogens**
Immunogen#1 AUG1-CLDK	**C-LDKFLIKNSNDF SEQ ID NO: 30**	**SEQ ID NO: 25; and SEQ ID NO: 28**
Immunogen#2 AUG2-KKLE	**KKLEKVKAYR-C SEQ ID NO: 31**	**SEQ ID NO: 22 SEQ ID NO: 23 SEQ ID NO: 27**
Immunogen#3 AUG3-CKNS	**C-KNSVVEASEAAYKEA SEQ ID NO: 32**	**SEQ ID NO: 3 SEQ ID NO: 4 SEQ ID NO: 5 SEQ ID NO: 24**

3.3 **Example 2** of the present application tests the cross-reactivity of the mAbs of the present application. It is found that four of the selected hybridomas bind to and recognize 14-3-3 eta isoforms at two serial dilutions but not with any other isoform even at lower dilution showing that the claimed mAbs are highly specific for the 14-3-3 eta isoform. – See **last 3 lines on page 107 of the appeal and first two lines on page 108 of the appeal and table 4b on page 109 of the appeal**).

3.4 **Example 3 and Figure 5** on the other hand show that polyclonal antibody raised against a 12 amino acid peptide from the N-terminus of 14-3-3 eta (same as the commercial polyclonal antibody, SA476 0100 available from Biomol International LLP) cross-reacts with other isoforms, particularly, the gamma isoform. – **See Para [00208] on Page 109 of the appeal**. A highly similar sequence from the N-terminus of the sheep 14-3-3 eta protein (BDREQLLQRARZ) was used in D4 and D5 for generating antibodies. The antibodies of D4 and D5 are therefore, similar to the commercial antibody from Biomol International LLP- **See paras 5-8 of Dr. Anthony Marotta's declaration on pages 348 to 349 of the appeal**.



3.5 **Example 4** demonstrates the ability of the monoclonal antibodies of the present application to bind 14-3-3 eta in its

native configuration. The mAbs of the present application immunoprecipitate both endogenous (HeLA cell derived 14-3-3 eta in the example) and recombinant 14-3-3 eta. – **See paras [00210] and [00210] on pages 109-110 of the appeal**

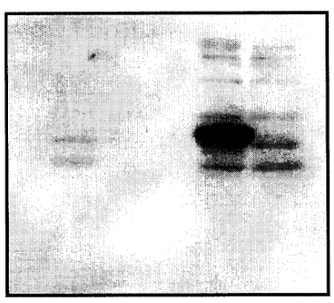


FIG. 6

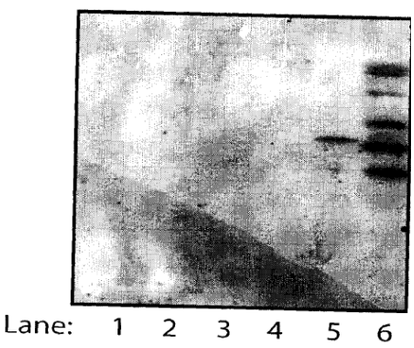
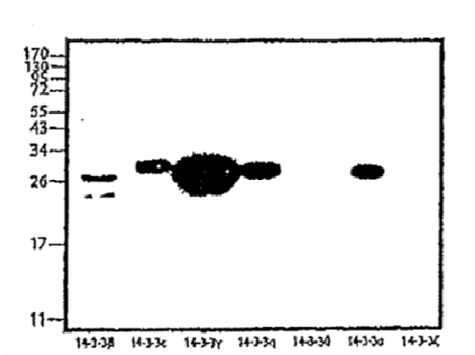


FIG. 7

4. Additional data submitted during the prosecution of the application: In addition to the aforesaid data provided in the complete specification of the present application, the Applicant also submitted a report by SignalChem which characterizes two commercially available antibodies, namely, antibody cat#sc-17287 from SantaCruz Biotechnology (used in document D1 cited in the hearing notice) and antibody cat#IB18645 from Immuno-Biological Laboratories (used in documents D2 and D3 cited in the hearing notice). The report tests the cross-reactivity of the aforesaid commercially available antibodies with the seven14-3-3 protein isoforms and determines that none of the said antibodies is specific to the 14-3-3 eta isoform.



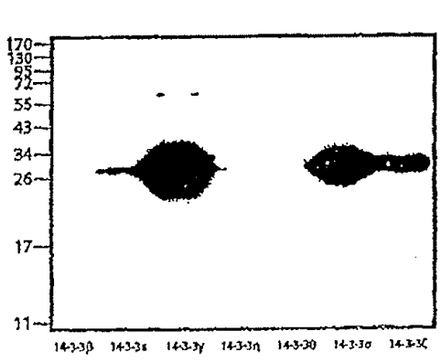


Fig 1: Ab cat#sc-17287 from SantaCruz Biotechnology Fig 2: Ab cat#IB18645 from Immuno-Biological Laboratories

5. **Data submitted with Dr. Anthony Marotta's declaration:** A declaration by Dr. Anthony Marotta submitted during the prosecution of the corresponding U.S application was also filed with the hearing submissions. Said declaration establishes that the antibody of documents D4 and D5 cited in the hearing notice is raised against an epitope (GCREQLLQRARZ) that is highly similar to the epitope of the polyclonal antibody commercially available from Biomol International LLP (raised against DREQLLQRARLA) and the slight difference are restricted to each peptide termini and are likely species related, but the overall sequences are identical. Dr. Marotta shows through **Appendix A**:

   (i) that the Biomol antibody does not show specificity for 14-3-3- eta over other isoforms and cross-reacts, particularly, with the gamma isoform. –See **page 351 of the appeal**

   (ii) that the Biomol antibody does not bind to 14-3-3- eta in its native configuration as it is shown useful for immune-blotting (western blot) but not immunoprecipitation (para 3 of Marotta's declaration on **page 348 of the appeal**).- **See page 352 of the Appeal**

Dr. Marotta concludes that the results with the Biomol antibody are persuasive in demonstrating that that the cited art antibodies would not exhibit selectivity for the human 14-3-3 eta protein over the other 14-3-3 isoforms. – **See paras 5 to 8 on pages 348 and 349 of the appeal**.

Dr. Marotta also concludes from Appendix A that there is a clear unmet need for monospecific anti-14-3-3 eta antibodies capable of

immuno-precipitating endogenous 14-3-3 eta in its native configuration. – See **para 3 on page 348 of the appeal**

6. The appellant has provided their explanation for the grounds of the refusal order as under:

6.1 GROUND 1 OF REFUSAL:

6.1.1 The amendments for addition of claims 9-21 and 28-30 are not allowable under section 59 of the Patents Act.

RESPONDENT'S FINDINGS- Page 52 of the Appeal

"*Explanation given to objection no 1 is not satisfactory and retained for amended claims 9-21 and 28-30. The amendments for addition of claims are not allowable as per section 59 of the Patents Act, 1970. Moreover these claims are not technically supported by the description. The specification provides only a vague speculation regarding the claimed sequences and its specificity.*"

6.1.2 The Respondent erred in holding that the amended claims 9-21 and 28-30 were not in accordance with Section 59 of the Patents Act as amendments for addition of claims is not permitted under Section 59 of the Indian Patents Act, 1970 and that the said claims were not technically supported by the description which provides only a vague speculation regarding the claimed sequences and their specificity.

6.1.3 The Respondent erred in deciding:

a. whether the said addition of new claims is by way of clarification, explanation or disclaimer or not; and

b. whether the said revisions enlarge the scope of the claims and description as originally filed.

6.1.4 At the outset, all claim amendments filed by the Appellant were within the scope of the claims and specification as originally filed and no new matter was added. The new dependent claims 9-21 and 28-30 (see Pages 334-336 of the appeal) did not enlarge the scope of the original claims as originally filed, were supported by the description and claims and were meant for specific claiming by way of clarification. Support for the amended claims was provided to the Respondent in the hearing submissions (see Pages 318 to 319 of the appeal) and is again provided as follows:

Rejected claim no.	Support in PCT claims	Support in specification
Claim 9	Claim 6	Para [0054] and table 1 in para [0184]
Claim 10	Claim 5	Para [0086] and table 1 in para [0184]
Claim 11	Claim 5	Para [0086] and table 1 in para [0184]
Claim 12	Claim 5	Para [0086] and table 1 in para [0184]
Claim 13	Claim 5	Para [0086] and table 1 in para [0184]
Claim 14	Claim 6	Para [0088] and table 1 in para [0184]
Claim 15	Claim 5	Para [0086] and table 1 in para [0184]
Claim 16	Claim 5	Para [0086] and table 1 in para [0184]
Claim 17	Claim 5	Para [0086] and table 1 in para [0184]
Claim 18	Claim 4	Para [0083] and table 1 in para [0184]
Claim 19	Claim 6	Para [0088] and table 1 in para [0184]
Claim 20	Claim 6	Para [0088] and table 1 in para [0184]
Claim 21	Claim 6	Para [0088] and table 1 in para [0184]
Claim 28	Claim 1	Paras [0058], [00105] and Example 1

Claim 29	Claims 1 and 16	Paras [0058] and [00105]
Claim 30	Claims 1 and 16	Paras [0093] and [0095] and Example 1

6.1.5 It is submitted that the Appellant, in order to further define the invention by way of explanation, for the purpose of specific claiming, added dependent claims 9-21 and 28-30. Said dependent claims are within the ambit of the claims and specification as filed as is apparent from the table above. Claims 9 to 21 specifically claim antibodies that are capable of binding to an epitope comprising an amino acid sequence of SEQ ID Nos. 24, 3, 4, 5, 10, 29, 1, 8, 9, 11, 22, 23 and 27, respectively. Claims 4, 5 and 6 of the application as filed relate to antibodies that are capable of binding to an epitope comprising an amino acid sequence of SEQ ID Nos. 11 to 16, SEQ ID Nos. 1 to 10 and SEQ ID Nos. 17 to 32, respectively- See page 118 of the appeal. Clearly, claims 9 to 21 are fully within the scope of claims as filed.

6.1.6 Also, claims 28, 29 and 30 further narrow the scope of claim 1 by specifying that the antibody is a murine antibody, a humanized antibody and is produced by a hybridoma. Since claim 1 of the application as filed (see page 118 of the appeal) does not limit the nature of the antibody claimed, claims 28, 29 and 30 are within the scope of said claim. Moreover, humanized antibodies of refused claim 29 are specifically claimed in claim 16 of the application as filed (see page 119 of the appeal). Further, murine (relating to mice or rodents)

antibodies of refused claim 28 are specifically supported by example 1 where the antibody was prepared by immunizing mice. The humanized antibodies of claim 29 are fully within the scope of claim 16 as filed, since claim 16 also covers humanized antibodies. Further, the antibodies produced by hybridoma of claim 30 are supported, not just by claim 1 as filed but also by Example 1 which shows producing monoclonal antibodies through hybridomas.

6.1.7 The Controller's assertion that "*Moreover these claims are not technically supported by the description. The specification provides only a vague speculation regarding the claimed sequences and its specificity.*" is absolutely incorrect. Each of the epitopes against which antibodies of claims 9-21 which have been raised, are described in the experimental section in table 1 in para [0184] on page 104 of the appeal. Example 1describes the production of antibodies using epitopes of immunogen 1 of SEQ ID NO 30 (which shares sequence similarity with epitopes of SEQ ID NOs. 25 and 28), immunogen 2 of SEQ ID NO: 31 (which shares sequence similarity with epitopes of SEQ ID NOs. 22, 23 and 27) and immunogen 3 of SEQ ID NO: 32 (which shares sequence similarity with SEQ ID NOs: 3, 4, 5 and 24) has been provided in Example 1 and the specificity of the antibodies generated through said antigens has been tested in Example 2. The ability of the antibodies to bind to the 14-3-3 eta isotope in its

native configuration is provided in Example 4. Therefore, there is no vague speculation regarding the claimed sequences and their specificity.

6.1.8 Sections 57 and/ or 59 of the Patents Act do not bar addition or deletion of claims. Therefore, the finding of the Respondent that the addition of claims is not allowed under Section 59, is bad in law. By the same analogy of the Respondent, if it is assumed to be correct, even deletion of claims should not be allowed as deletion of claims does not find mention in Section 59 and deletion of claims would enlarge the scope. Such an interpretation of the "amendment provisions" is not just absurd but also against the spirit of affording a fair chance to the applicant to properly claim their invention.

6.1.9 The Respondent clearly ignored:

i. That claims 9-21 and 28-30 are dependent claims;

ii. That the law in India in relation to dependent claims is clear- dependent claims always "NARROW" the scope of the claims and don't have the effect of enlarging the scope. Reliance is placed on the following case law and guidelines:

a. *Para 34(xi) of the order of Division bench of the Hon'ble Delhi High Court in F. Hoffmann-La Roche Ltd. & Anr. Vs. CIPLA Ltd.* which states that "Where claims are 'dependent'

it incorporates by reference 'e*verything in the parent claim, and adds some further statement, limitations or restrictions".*

b. Clause 05.03.16 (q) at page 43 of the Manual of the Patent Office Practice and Procedure that clearly states that "*A dependent claim derives antecedence from an independent claim and reads into it the features of the independent claim and may contain optional features."*-

iii. That neither is the scope of the originally filed claims enlarged in view of the said addition of new dependent claims nor are the new dependent claims introducing matter in the specification which was not part of the original description.

a. Reliance is placed on The Decision of the Hon'ble Delhi High Court in AGC Flat Glass Europe SA v/s Anand Mahajan & Ors., wherein the Hon'ble Court in para 17 clearly states that *"the scope of enquiry in relation to amendments in the patent claim is limited to the extent as to whether it introduces any new claim which extends the scope of the monopoly rights of the patentee."*

b. Reliance is also placed on Para 23 of the order of the Hon'ble IPAB in OA/7/2016/PT/MUM dated 12th October 2020:

"*Now as both the amendments are not forming part of any newly introduced matter in the speciation rather they are part and parcel of the original disclosure in the complete specification, they do not attract the provisions of section 57 read with section 59; as they do not go beyond the originally filed specification and were made as 'explanation' fulfilling the criterion of amendments as per the teachings of section 57 read with section 59 of the Patents Act, 1970.*"

6.1.10 It is submitted that on a plain reading of Section 59, it is very clear that there is no bar with regard to addition of (a) new claims, (b) deletion of claims and (c) merging of claims. The only criteria that has to be looked into is whether the scope of the claims is enlarged or not by the said addition, deletion or merging of claims.

6.1.11 In view of the above, it is respectfully submitted that clearly the Respondent failed to appreciate and understand the purport of the expression "scope" in Section 59.

6.1.12 From claims 9-21 and 28-30, the Hon'ble IPAB would appreciate that said claims further and specifically define the antibody referred to in claim

1, and there is adequate support for said claims not just in the claims as filed but also in the complete specification of the present application. Accordingly, this ground of refusal does not apply.

6.2 **GROUND 2 OF REFUSAL:**

6.2.1 **The subject matter of the claims are products of nature and are not patentable under section 3(c) of the Patents Act.**

RESPODENT'S FINDING: "*the explanation and amendment of claims 1 and 31 is not found to be persuasive. The amendment to the claim 1 by the addition of the word a 'non- human monoclonal' and by omitting the word "isolated" from in claim 31 and does not make the product patentable under section 3 (c) of the Patents Act, 1970.*

These amendments makes the claim broader in scope than the earlier claim, as it encompasses all non-human and isolated as well as the non-isolated ones existing anywhere. The objection 2 of hearing notice has not been met as the amended claims claiming for an anti-14-3-3 antibody which is not patentable as per the provisions of clause (c) of section 3 of the Patents Act, 1970. The claimed subject matter in these claims is the discovery of the naturally existing antibody which are isolated. It is concluded that isolated anti-14-3-3 antibody was ineligible for patent protection as a product of nature."

See page 52 of the appeal

MONOCLONAL ANTIBODIES ARE NOT SUBSTANCES OCCURING IN NATURE AND DO NOT FALL WITHIN THE AMBIT OF SECTION 3(c) OF THE PATENTS ACT

6.2.2 The monoclonal antibodies claimed in the present application are not substances occurring in nature but are very much products of human ingenuity.

6.2.3 Firstly, the specific epitope fragments identified by the Appellant (5-20 amino acids) do not occur in nature per se but are part of a bigger protein (246 amino acids in length). Therefore, monoclonal antibodies against said shorter peptide fragments do no occur in nature but have been created by the Appellant by identifying and designing specific antigens.

6.2.4 Antibodies do not occur in nature in the monoclonal form but are present as a polyclonal pool. The claimed monoclonal antibodies have not been isolated from a pre-existing natural pool of antibodies. The Respondent has also not provided any reason or evidence to show that the claimed antibodies are derived from a natural pool. Thus, the claimed antibodies are not substance occurring in nature.

6.2.5 The monoclonal antibodies claimed are produced by hybridoma technology which utilizes a man-made cell comprising a fusion of spleen cells with myeloma cells, that is, a hybridoma cell- **See Page 107 of the Appeal**. Hybridomas do not occur in nature. Accordingly, monoclonal antibodies

produced by hybridomas cannot be substances occurring in nature.

6.2.6 Moreover, the claimed antibodies have a different selectivity profile than what exists in nature, they necessarily also have different structural (e.g, different amino acid sequences and three-dimensional structures) and functional (e.g, bind to different antigens) characteristics. These difference rise to the level of a marked difference, and so the claimed antibodies are not 'living or non-living substances occurring in nature'.

6.2.7 Thus even without the limitation of a "non-human" monocolonal antibody, the antibodies claimed in the present application were not products of nature. However, the limitation of "non- human" monocolonal antibody as specified in the refused claims further distances the monoclonal antibodies claimed from products of nature as the specific human 14-3-3η antigenic peptide does not occur naturally in non-human sources and antibodies to the same cannot and do not occur in non-human sources. As a composition resulting from a **scientifically-induced cross-species immunological interaction**, the antibody composition as claimed clearly cannot and does not occur in nature.

6.2.8 Therefore, the Respondent very much erred in holding that "*The amendment to the claim 1 by the addition of the word a 'non- human monoclonal' and by omitting the word "isolated"*

from in claim 31 and does not make the product patentable under section 3(c) of the Patents Act, 1970".

6.2.9 The antibodies of the instant application were not known prior to the instant application and the invention claimed in the instant application was the first to identify an anti-14-3-3 antibody exhibiting the requisite selectivity for human 14-3-3 eta over other human 14-3-3 protein isoforms and specifically binding to the disclosed amino acid sequences (see Table 1). In fact, as demonstrated by data submitted during the prosecution of the instant application, commercially available anti- 14-3-3-η antibodies were shown to be cross-reactive to other 14-3-3 isoforms due to the highly conserved nature of the 14-3-3 family of proteins and do not compare to the highly specific 14-3-3-η antibodies of the instant application.

6.2.10 Even following the strict United States case law and the USPTO Eligibility Guidelines for examination of nature-based products, the antibodies of the instant application are considered patentable. The U.S. case law and the USPTO guidelines **expressly require an evidence that such an antibody is naturally-occurring**. In particular, example 8 of the USPTO Eligibility explicitly indicates:

6.2.11 *Some murine antibodies to Protein S occur in nature, and it is possible that nature might*

randomly create a murine antibody having the CDR sequences of SEQ ID NOs: 7-12. ***But unless the examiner can show that this particular murine antibody exists in nature, this mere possibility does not bar the eligibility of this claim****. See, e.g., Myriad, 133 S. Ct. at 2119 n.8 ("The possibility that an unusual and rare phenomenon might randomly create a molecule similar to one created synthetically through human ingenuity does not render a composition of matter non-patentable" (emphasis in original)). Because the claimed antibodies have different CDRs than what exists in nature, they have different structural (e.g., different amino acid sequences and three-dimensional structures) and functional (e.g., bind to different antigens) characteristics. These differences rise to the level of a marked difference, and so the claimed antibodies are not "product of nature" exceptions. Thus, the claim is not directed to an exception (Step 2A: NO), and qualifies as eligible subject matter.*

https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf

6.2.12 Further monoclonal antibodies are considered patentable by the Indian Patent Office also.-

i. See **Annexure A8 at page 377 of the appeal,** particularly, patent numbers 252161 and 254036 **on page 378** which relate to antibodies by sequence of the epitope.

ii. See also **Annexure A9 starting at page 384 of the appeal** which shows more than 800 patents granted in the field of antibodies.

6.2.13 The Respondent has also erred in holding that "***These amendments makes the claim broader in scope than the earlier claim****, as it encompasses all non-human and isolated as well as the non-isolated ones existing anywhere"* Emphasis added

6.2.14 By amending the claims to recite non-human antibodies, the Appellant has in fact narrowed and not broadened the scope of the application as all human antibodies are excluded from the scope of patentability. In contrast the claims as filed related to 'antibodies' which encompass both human and non-human antibodies. Again the as filed claim has no restriction in relation to isolated and non-isolated antibodies. Therefore, this cannot be a concern in determining any change in claim scope. (**See page 118 of the Appeal for as filed claim 1**).

6.3 **GROUND 3 OF REFUSAL:**

6.3.1 Claims 32-33 are not supported by working examples and the claims are not supported by the description.

RESPODENT'S FINDING: "*Explanation given to* ***objection no 4 and 6*** *are not found be persuasive.*

The applicant had opined that the

exemplification of the claims is not even mentioned as a criteria for patentability under the Indian Patents Act. So long as the claimed invention can be easily understood and worked by the person skilled in the art from a reading of the specificaion, the claims will be considered to be sufficiently described by the specification.

In applications directed to inventions in the unpredictable arts (biological, chemical, and pharmaceutical inventions,), the disclosure of a single species usually does not provide an adequate basis to support generic claims. Technology involving unpredictable factors, such as most reactions and physiological activity, may require more for enablement. A single example may suffice, but if the claims cover a broad field, the application must include multiple examples extending over the entire range of claimed subject-matter in order to satisfy 10(4)(a) & (b) of the Patent Act, 1970.

The examples described in the instant application described only the biological experimental evidences showing the antibodies against immunogen # 1 -4 (Sq ID 30, 31, 32 and 33)and not cross reactive with six other isoforms. Since none of the working examples provide ample evidence to specificity, the description is insufficient to substantiate the

instant invention. No working examples are provided to prove that the anti-14-3-3 antibodies do not bind 14-3-3 eta protein in its natural configuration

The amended claims 1-33 and description refers to the function of the antibodies recognizing epitopes of given sequences. The antibodies are characterized by its inherent characters not with its technicaI features.

Amended claim 32 refers to making of an antibody, which is not clear with technical description and also not exemplified. Also this claim refers to introducing to a mammal with a peptide, which falls within the scope of 3(i) of the Patent Act, 1970.

Amended claim 33 refers to a kit which must be characterized by its technical features. The instructions for use recited in the said claim are to be considered as relating to presentation of information and therefore are not a technical feature of that kit and do not limit the scope of such claim.

Amended claims 32 & 33 do not define any technical features of the invention."

6.3.2 Sufficiency has to be looked through the eyes of a person skilled in the art who possesses common general knowledge and based on his common general knowledge and disclosure contained in the patent specification is able to carry out the

claimed invention without undue experimentation. Just like India, the law in US, China, Europe and Australia requires that the disclosure should be sufficient to enable a person skilled in the art to work the invention.

6.3.3 Sufficient experimental evidence is provided in the specification for a person skilled in the art to work the invention. The epitopes designed by the Applicant are identified in the experimental section in table 1 in para [00184] (**See pages 104 and 105 of the appeal**).

i. **Example 1** shows that antibodies were raised against immunogens # 1-4 (SEQ ID 30, 31, 32 and 35). Of these immunogen#1 of SEQ ID NO: 30 is similar to immunogens of SEQ ID NOs: 25 and 28, immunogen#2 of SEQ ID NO: 31 is similar to immunogens of SEQ ID NOs 22, 23 and 27 and immunogen#3 of SEQ ID NO: 31 is similar to immunogens of SEQ ID NOs: 3, 4, 5 and 24. Thus the results shown in relation to immunogens# 1, 2 and 3 of SEQ ID NOs: 30, 31 and 32 can be reasonably extrapolated at least to SEQ ID NOs: 3, 4, 5, 22, 23, 24, 25, 27 and 28. Therefore, it is expected that antibodies said sequences shall demonstrate a similar profile as antibodies to SEQ ID NO: 30, 31, 32.

ii. The method of production of the claimed antibodies using hybridomas has also been elaborated in Example 1. (See **pages 106 to 107 of the appeal**)

iii. **Example 2** shows that the antibodies obtained in Example 1 showed specificity for the 14-3-3 eta isotype at two dilutions and did not cross-react with other 14-3-3 isotypes even at a higher dilution. (See **Table 4b at para [00205] on page 109 of the appeal**)

iv. **Example 4** shows that the antibodies claimed in Example 1 bind to both 14-3-3 eta protein obtained from the cell supernatants from lysed HeLA cells and human recombinant 14-3-3 eta protein. This shows that the anti-14-3-3-η antibodies obtained in Example 1 do in fact bind the 14-3-3-η protein in its natural configuration. (See **Paras [00209] to [00212] on pages 109 and 110 of the appeal**)

v. **Example 3 and Figure 5**, on the other hand show that commercially available antibodies raised against the N-terminus peptide of 14-3-3 eta, namely, Ac-DREQLLQRARLA, do not show specificity for 14-3-3 eta and cross-react with other 14-3-3 isoforms, particularly, 14-3-3 gamma. (**See paras [00206] to [00208] on page 109 of the appeal**)

6.3.4 The Respondent's observation that 'none of the working examples provide ample evidence to specificity' is incorrect. As discussed above, Example 2 provides data on specificity. The Respondent itself admits in the order that 'the examples described in the instant application described only the biological experimental evidences showing the antibodies against

immunogen # 1-4 (SEQ ID NO: 30, 31, 32 and 35) and not cross reactive with six other isoforms.' Thus there is data available in the specification regarding specificity of the antibodies of the present application and there is sufficient data available to cover all aspects of the present application.

6.3.5 Further, the Respondent's finding that 'no working examples are provided to prove that the anti-14-3-3 antibodies do not bind 14-3-3 eta protein in its natural configuration' is absurd and is based on an incorrect understanding of the present application. It has **never** been the Appellant's stand that the 14-3-3-eta antibodies of the instant application do not bind the 14-3-3 eta protein in its natural configuration. In fact, the Appellant through the instant application provides antibodies that **bind to** both recombinant 14-3-3 eta protein and to 14-3-3 eta protein in its natural configuration (**See Example 4 on pages 109 and 110 of the appeal**) but do not bind to the other isoforms of the 14-3-3 protein. Thus an expectation that the Appellant should have provided data in the complete specification to establish that the anti-14-3-3 antibodies do not bind 14-3-3 eta protein in its natural configuration is absurd and incorrect.

6.3.6 Finally, so long as there is data provided in the complete specification to support the Appellant's claim, the requirement to provide data for each

and every embodiment does not arise. Patent specifications are not production documents or experimental records. Therefore, an expectation that data be provided for each and every embodiment claimed is unreasonable.

6.3.7 Examples are only meant to illustrate the working of the invention and, since the specification is addressed to the person skilled in the art, not everything needs to be exemplified. So long as the claimed invention can be easily understood and worked by the person skilled in the art from a reading of the specification, the claims will be considered to be sufficiently described by the specification. There is sufficient data provided in the complete specification to work the invention and to establish the Appellant's claim. Therefore, the question of lack of support in the description for want of working examples does not arise.

6.3.8 The Respondent has further observed that the antibodies are characterized by the function of the antibodies recognizing epitopes of given sequences, that is, their inherent character and not by their technical features. This observation of the Respondent is also based on an incorrect understanding of the invention claimed in the present application.

6.3.9 The ability of the antibody claimed to bind to specific epitopes is based on the antigens used for generation of the antibodies. Therefore, said ability is not inherent but has been tailored by the

selection, designing and use of specific antigens/epitopes for the generation of the antibody. Therefore, the antibody is defined by its specific technical feature which is specific binding to 14-3-3 eta, lack of cross reactivity with other 14-3-3 isoforms and ability to bind the specific epitopes defined. Thus the claimed antibody has not been defined by the functional features only but through a technical feature.

6.3.10 There are several ways which antibodies can be claimed. The article at page 411 of the appeal provides that antibodies can be claimed by way of the epitope too.

6.3.11 **Further cases granted by the Indian Patent Office show that antibodies can be defined by way of their epitopes- See Annexure A11 starting at page 420 of the appeal**, which shows:

a. Patent nos. 251532 (1899/MUMNP/2007) and 230716 (2592/CHENP/2005) defined through epitope sequences;
b. Patent nos. 254039 (2581/KOLNP/2006) and 245214 (1540/KOLNP/2006) defined through antigenic sequences; and
c. Patent Nos. 272873 (4482/CHENP/2010), 235930 (774/KOLNP/2006) and 243960

(3239/CHENP/2006) defined through functional properties.

6.3.12 The Respondent has further observed that claim 33 refers to a kit not defined by its technical features. It is submitted that Claim 33 is clearly defined by its technical feature which is the antibody of the specific 14-3-3 eta antibodies of the preceding claims. The novelty and inventive step of the kit is derived from the novel and inventive antibodies of the present application and not from the instructions for use objected by the Respondent.

6.3.13 The Respondent also erred in holding that amended claims 32 and 33 do not define any technical features of the invention. Claim 32 recites a method for making the 14-3-3 eta antibodies of the present application by introducing a peptide selected from the group of SEQ ID NOs: 1-32 which yield the specific 14-3-3 eta antibodies of the present application. Once the epitope sequence is identified a person skilled in the art can easily produce the antibody using that particular epitope based on his common general knowledge. In fact the method of production of the antibody is provided in detail in Example 1 of the specification. Therefore, the technical feature is clearly defined. Claim 33 recites a kit comprising the novel and inventive 14-3-3 eta protein specific antibodies of the present application. The novel and inventive antibodies are the primary technical

feature of the kits claimed. Therefore, the technical features are clearly defined. Thus in each of the rejected claims 32 and 33, the technical features are clearly defined.

6.4 **GROUND 4 OF REFUSAL:**

6.4.1 **Claim 32 is not patentable under section 3(i) of the Patents Act**.

RESPONDENT'S FINDING: "*Amended claim 32 refers to making of an antibody, which is not clear with technical description and also not exemplified. Also this claim refers to introducing to a mammal with a peptide, which falls within the scope of 3(i) of the Patent Act, 1970.*

CLAIM 32 IS NOT A METHOD OF TREATMENT, DIAGNOSIS, PROPHYLAXIS OR ANY OTHER METHOD RELATED TO THE TREATMENT OF HUMANS OR ANIMALS TO RENDER THEM FREE OF DISEASE OR TO INCREASE THEIR ECONOMIC VALUE

6.4.2 At the outset, this objection was neither raised in the hearing notice nor during the hearing. Therefore, the rejection of claim 32 under section 3(i) is unjust as the Appellant was not given an opportunity to address said objection. This act of the Respondent is against the principles of natural justice.

6.4.3 Further, the method of making the claimed monoclonal antibody is clear and exemplification

for the same is provided in Example 1 of the present application.

6.4.4 The Respondent has erred scientifically in holding that claim 32 "*refers to introducing to a mammal with a peptide, which falls within the scope of 3(i) of the Patent Act, 1970***."** Claim 32 is directed to a method for preparing a monoclonal antibody. The said method is a "biotechnological process" of preparing antibodies (recombinant biotechnology) that requires a mammal (such as laboratory bred BALB/c mice as seen from Example 1). Said step is essential in the production of monoclonal antibodies by hybridoma technology

6.4.5 Since the introduction of the peptide into the mammal as required by claim 32 is not intended for diagnosis, treatment or prophylaxis of a host but is meant for production of antibodies, the method of claim 32 cannot be treated to fall within the scope of section 3(i) of the Patents Act.

6.5 **GROUND 5 OF REFUSAL:**

6.5.1 **Claims 1-33 lack inventive step**

RESPONDENT'S FINDING: "*Antibodies which specifically bind to 14-3-3 antibodies were already known in the art, which was evident from D1 to D5.*

D1 discloses an anti-14-3-3 eta polyclonal antibody that specifically binds to human 14-3-3 eta protein in its natural configuration, wherein said antibody does not bind

to an epitope located at the N- terminus of human 14-3-3 eta and which further exhibits selectivity for 14-3-3 eta over the other 14-3-3 protein isoforms. The anti-14 -3-3 eta antibody of D1 inherently binds to an epitope comprising either a 14-3 -3 eta helix peptide or a 14-3-3 eta non-helix peptide and further would be suitable for use in treating arthritis in a patient. D2 and D3 each disclose an anti-14-3-3 eta polyclonal antibody that specifically binds to human 14-3-3 eta protein in its natural configuration, wherein said antibody exhibit s selectivity for 14-3-3 eta over the other 14-3-3 protein isoforms. The antibody of D2 and D3 is capable of immune precipitating 14-3-3 eta from a biological solution and has utility in immunohistochemistry. Moreover, the anti-14-3 -3 eta antibody of D2 and D3 inherently binds to an epitope comprising either a 14-3-3 eta helix peptide or a 14-3-3 eta non-helix peptide and further would be suitable for use in treating arthritis in a patient.

Amended claims 1-33 lack an inventive step in view of any one of D1 -D3 when combined with D4 or D5 and common knowledge in the art. D1-D3 each discloses an anti-14-3-3 eta antibody that specifically binds to human 14-3-3 eta protein in its natural configuration. D4 and D5 each disclose that elevated levels of 14-3-3 eta protein are present in the synovial fluid and serum of patients with arthritis. The skilled person would therefore be motivated to use common method of the corresponding technical field and hence the claims lack inventive step over the documents D1 -D5. Since the prior art documents discloses the 14-3-3 isoforms and identifying isoform specific

epitopes to generate isoform selective antibody, the instant invention is obvious to a person skilled in the art."

6.5.2 The Respondent has erred in their inventive step analysis for the following reasons:

i. **Failure to apply the correct test of obviousness**: The closest prior art was not identified by the Respondent. Further the assessment of the prior art along with the other teachings not conducted from the perspective of a person skilled in the art who has to be motivated to combine teachings of the prior art and must have reasonable expectation of success. Where the prior art does not give any direction to the invention the prior art cannot be said to obviate the invention in question.

ii. The Respondent did not take into consideration the data on the improved specificity of the antibodies of the present application for 14-3-3η as compared to antibodies used in the prior art which clearly establishes the inventive step of the claims of the present application. There is no reason provided why said data was not considered or how it does not establish the inventive step of the claims of the present application.

6.5.3 The Respondent held that antibodies that specifically bind to 14-3-3 antibodies were known in the art. This observation incorrect as the invention claimed in the present application is directed to antibodies that specifically bind to the

14-3-3 eta protein and not to 14-3-3 eta antibodies.

6.5.4 Even if the Respondent by said statement is trying to imply that antibodies specific to the 14-3-3 eta protein were known in the art, this observation is incorrect. The Appellant presented data to demonstrate that the antibodies known in the art were not specific to the 14-3-3 eta protein but demonstrated cross-reactivity with other 14-3-3 isoforms. The Respondent has not provided any reason why said data was not considered.

6.5.5 The Respondent's reasoning for lack of inventive step is based on an incorrect understanding of the problem addressed and solution provided by the invention claimed in the present application.

6.5.6 The problem addressed by the present invention was not to provide just any 14-3-3 eta antibody but anti 14-3-3 eta antibodies which are highly specific for the 14-3-3 eta protein and do not cross react with other 1-3-3 isoforms and which bind to 14-3-3 eta in its native configuration. The solution provided is antibodies that specifically bind to the 14-3-3 eta protein in its natural configuration and is capable of binding to an epitope comprising an amino acid selected from the group consisting of SEQ ID NOs: 1-32.

6.5.7 Unlike the observation of the Respondent, none of the cited prior art teaches antibodies which exhibit selectivity for the 14-3-3 eta protein over other 14-

3-3 isoforms. The following commercially available antibodies are disclosed in the prior art:

Antibody	**Covered by prior art**	**Cross reactivity established in**	**Binds to**
sc-17287 of Santa Cruz Biotechnology, Inc.	**D1 (DiFede et al.)** - P. 62 of document compilation, table, third last entry	SIGNALCHEM document submitted with the hearing submissions and with the reply to the FER	14-3-3 beta, epsilon, gamma and sigma
Cat#IB18645 of Immunobiological Laboratories	**D2 (Sato et al.)**- P. 76 of the document compilation, under materials and methods, 1st para, 4th last line **D3 (Satoh et al.)**- P. 81 of the document compilation, 1st column, 2nd para, lines 14-16	SIGNALCHEM document submitted with the hearing submissions and with the reply to the FER	14-3-3 epsilon, gamma, sigma and zeta
SA476-0100 of Biomol	D4 and D5 (P. 114 of the document compilation, lines 24-30) (Martin et al.whose Abs are used in D5 talk of antibodies to a similar epitope (Ac.GDREQLLQRARZ) as that used for the generation of Biomol's SA476-0100 (Ac-DREQLLQRARLA))	1. Complete specification, page 37, Fig 4, Example 3 2. Dr. Marotta's US declaration read with Exhibit A	14-3-3 Gamma Also Exhibit A of Marotta's declaration show that the Biomol Antibody does not bind to 14-3-3 eta in its native configuration

6.5.8 Thus clearly, the antibodies disclosed in the prior art are cross reactive with other 14-3-3 protein isoforms and are not specific for the 14-3-3 eta protein. In contrast example 2 of the present application establishes that the antibodies of the

present application do not cross react with other 14-3-3 isoforms and are specific for the 14-3-3 eta protein.

6.5.9 None of the prior art provides any motivation to design antibodies based on the antigens disclosed in the present application. None of the prior art suggests that antibodies derived from the antigens of the present application will be highly specific for the 14-3-3 eta protein.

6.5.10 In fact the prior art does not even recognize the need for 14-3-3 eta selective antibodies and mischaracterizes in D1 that the antibody disclosed therein (antibody sc-17287) is not cross-reactive to other isoforms. See, e.g., id., at page 125, end of 2nd column and table 1 cf SIGNALCHEM, at Figure 1 (demonstrating that sc-17287 also binds 14-3-3 beta, epsilon, gamma, and sigma isoforms). Thus based on the teaching of D1 one of skill in the art would not even seek more specific 14-3-3 eta antibodies.

6.5.11 Thus, none of the prior art document taught, suggested or demonstrated the specific anti-14-3-3 eta antibodies of the instant application.

6.5.12 The cited references neither teach nor suggest an antibody capable of specifically binding to a human 14-3-3 eta protein in its natural configuration, wherein said antibody exhibits selectivity for said eta protein over other 14-3-3 isoforms.

6.5.13 Paragraph [004] of the instant application (on page 73 of the appeal) recognizes that commercially available anti-14-3-3 eta antibody preparations show cross-reactivity with other 14-3-3 isoforms and the limited number of 14-3-3 antibodies which recognize the 14-3-3 protein in its native configuration.

6.5.14 The instant application also characterizes the specificity of SA476 0100, a commercially available anti-14-3-3 rabbit polyclonal antibody raised against an N-terminus epitope of 14-3-3 eta available from Biomol International LP. Id., at Example 3 (See Para [00208] on Page 109 of the appeal). In marked contrast to the results obtained with the antibodies of the instant application, the results shown in Figure 5 demonstrate that SA476 0100 cross reacted with other 14-3-3 isoforms. Id., at Example 3, page 37, paragraphs [00206]-[00208] (on page 109 of the appeal).

6.5.15 Applicants also submitted with the reply to the first examination report as Annexure A, an independent third-party characterization by SIGNALCHEM of two commercially available antibodies (1) Antibody cat# sc-17287 available from SantaCruz Biotechnology, Inc. and (2) Antibody cat # IB18645 available from Immuno-Biological Laboratories which demonstrate that similar to the SA476-0100 antibody, the antibodies used in the cited references do not bind 14-3-3 eta protein in its natural configuration

and/or exhibit selectivity for human 14-3-3 eta protein over other human 14-3-3 protein isoforms. Figures 1 and 2 of the SIGNALCHEM document show that neither the antibody available from SantaCruz or Immuno-Biological Laboratories, respectively, exhibited selectivity for 14-3-3 eta protein over other 14-3-3 isoforms. (See page 343 of the Appeal)

6.5.16 Prior art D1, D2 and D3 rely on the use of the commercially available 14-3-3 eta antibodies characterized in the SIGNALCHEM document. D1 discloses use of antibody sc-17287 and mischaracterizes such antibody as not cross-reactive to other isoforms. See, e.g., id., at page 125, end of 2nd column and table 1 cf SIGNALCHEM, at Figure 1 (demonstrating that sc-17287 also binds 14-3-3 beta, epsilon, gamma, and sigma isoforms)- Page 343 of the Appeal. Both D2 and D3 use the anti-14-3-3 eta antibody from Immuno-Biological Lab Co. See, D2, at page 219, Materials and Methods, 1st paragraph and D3 at page 579, 1st column, 2nd paragraph and Table 1; cf SIGNALCHEM, at Figure 2 (showing that IB18645 also binds 14-3-3 epsilon, gamma, sigma and zeta isoforms)- Page 343 of the Appeal. Accordingly, the antibodies of the present claims were established by way of proper technical comparison, to be superior to and inventive over the antibodies of the prior art D1-D3.

6.5.17 The epitope targeted by D4 (Kilani) and D5 (WO 2007/128132) is the same as the commercial anti-14-3-3 eta antibodies produced by Biomol (SA476-0100) shown to be cross reactive with other 14-3-3 isoforms in the instant application. Thus, these prior art antibodies were shown to not exhibit selectivity for the human 14-3-3 eta protein over other human 14-3-3 protein isoforms as presently claimed.

6.5.18 The Kilani et al. and WO 2007/128132 references teach immunoblotting using anti-human 14-3-3 polyclonal antibodies according to Martin et al. (1993; FEBS Letters. 331:296-303) (see e.g. page 11, lines 26-30), which in turn teaches that antibodies against the acetylated N-terminal sequences of sheep 14-3-3 isoforms were raised in rabbits and wherein the antigenic peptide used for the eta isoform was Ac.GDREQLLQRARZ. (see page 297; Sec. 2.4) The sequence used by Martin et al. (Ac-GDREQLLQRARZ) is nearly identical to the immunogenic sequence used by Biomol (now Enzo) to generate its SA476-0100 antibody product (Ac-DREQLLQRARLA). Accordingly, one skilled in the art would recognize the antibodies disclosed in Kilani and WO 2007/128132 to share the same 14-3-3 isoform selectivity as the Biomol SA476-0100 antibody product based on generation from the same immunogenic sequence.

6.5.19 The instant application itself discloses a commercially available anti-14-3-3 rabbit polyclonal antibody raised against a 12 amino acid peptide (Ac-DREQLLQRARLA-NH2) epitope from the N-terminus of 14-3-3 eta (Biomol International LP, Cat. SA476-0100). However, as stated on page 37 of the application and shown in Figure 5 (Page 109 of the appeal), apparently this commercially available antibody against 14-3-3 eta cross reacted with other 14-3-3 isoforms, primarily gamma. Thus, Example 3 of the present application shows that antibodies directed against N-terminal epitope DREQLLQRARLA (polyclonal antibody preparation sold by Biomol) do not specifically bind human 14-3-3 eta protein and are not selective for 14-3-3 eta protein over other human 14-3-3 protein isoforms as required by present claim 1.

6.5.20 Further a declaration filed in corresponding U.S. application number 12/745,235 (which has been allowed) by Dr. Anthony Marotta was submitted with the reply to the first examination report as Annexure B. Said declaration confirms that the epitope targeted by the Kilani and WO 2007/128132 references is the same as the commercial anti-14-3-3 eta antibodies produced by Biomol (SA476-0100) and that tests with the Biomol antibody have shown it to be cross reactive with other 14-3-3 isoforms. For example, Dr. Marotta establishes that "[t]he sequence used by Martin et al. (Ac-GDREQLLQRARZ) is highly similar to the immunogenic sequence used by

Biomol (now Enzo) to generate its SA476-0100 antibody product (Ac-DREQLLQRARLA). The slight differences are restricted to each peptide termini and are likely species related, but overall the sequences are identical." (See Para 6 on Page 348 of the appeal). Appendix B and C enclosed with the declaration provide product data sheets for the Biomol SA476-0100 antibody and blocking peptide, respectively. (Marotta Declaration, para 6- Page 348 of the appeal) In characterizing the commercially available antibodies for selectivity and affinity to 14-3-3eta, Dr. Marotta describes the SA476-0100 antibody used in the cited prior art reference as lacking the ability to bind 14-3-3 eta protein in its natural configuration and/or exhibit selectivity for human 14-3-3 eta protein over other human 14-3-3 protein isoforms. Further, the data presented in Appendix A accompanying the Marotta Declaration demonstrates how the SA476-0100 antibody recognizes the gamma isoform in addition to the eta isoform. (Marotta Declaration, para 7- Page 349 of the appeal).

6.5.21 Considering the above, starting from any one of references D1-D5, the objective technical problem can be formulated as: How to provide 14-3-3 eta specific antibodies? The solution according to the instant application is neither disclosed, nor suggested, in any of the prior art documents, alone or in combination.

6.5.22 Based on the data and disclosure in the present application as well as evidence submitted along with the reply to the first examination report and the hearing submissions it was established that one of ordinary skill in the art would reasonably conclude that D1-D5 do not teach or suggest the invention as presently claimed. Accordingly, the claims of the instant application comprise an inventive step.

6.5.23 In view of the foregoing submissions it is clear that the instant application is inventive and clearly does not fall within the prohibitory ambit of section 3(c) or section 3(i) of the Patents Act, provides sufficient working examples and sufficient and clear disclosure in the complete specification for a person skilled in the art to work the invention and that all claim amendments are well supported by the claims as filed and the complete specification. None of the grounds of rejection raised by the Respondent is valid or applies to the claims of the instant application. In view of the same, the rejection of the instant application by the Respondent is wholly unjustified.

7. We have considered the submissions of the learned counsel of the appellant and analyzed vis- a-vis the order of learned Controller. On the issue of the amendment of claims, we partially agree with the appellant that the amendments were made for defining the claims in a better way and in their opinion; it was for narrowing the scope. But what made them not to consider all this aspects

prior to filing PCT International application, which was filed only with 26 claims and possible widest principal claim, which could accommodate many variations.

8. We still observe that the claims on record should be commensurate with the contribution made. We direct the appellants to file the amended set of claims incorporating the following amendments:

- The principal claim 1 shall be restricted with the feature(s) of claim 9;
- Claim 4 should be restricted to SEQ ID NO. 3-5
- Claim 5 should be restricted to SEQ ID 29 and 32
- Claims 3, 6, 7, 8, 13, 15-21 and 32 should be deleted.

9. We are of the opinion that for the reasons as explained by the appellant a "non- human" monocolonal antibody, do not attract the provisions of section 3(c) of the Patent Act, 1970.

10. We are also inclined to accept the arguments of the learned counsel of the appellant with regard to the official requirement of lack of inventive step. With restriction of claims as shown in para 8 above this requirement will further be obviated.

11. We direct the appellant to submit the amended set of claims to the respondent, within 3 weeks from the date of issuance of this order.

12. We, set aside the impugned order dated 07/12/2016 issued by the respondent, and direct the respondents to grant the patent on the amended set of claims, within 3 weeks from the submission of the amended set of claims.

13. Keeping in view the above facts and circumstances, the instant appeal is allowed. No cost.

-Sd/-

(Dr. B.P. Singh)
Technical Member (Patents)

-Sd/-

(Justice Manmohan Singh)
Chairman