

The Patents Act, 1970

Section 25(1)

In the matter of Application
for patent no. 93/DEL/2003

And

In the matter of representation
under section 25(1) of the
Patent Act, 1970 as amended
by Patent (Amendment) Act,
2005.

And

In the matter of rule 55 of the
Patent Rules, 2003, as amended by
the Patent (Amendment) Act, 2005.

M/s Yeda Research & Development Co, Israel ... The Applicant

M/s Natco Pharma Limited., India ... The Opponent

Hearing held on 24th June,2008

Present

Mrs. Ranjan Mehta Dutt Agent for the opponent

Sh. Koraijam

Sh. S. Majumdar Agent for the opponent

DECISION

A representation by way of opposition under section 25(1) of the Patent Act as amended by Patent (Amendment) Act 2005 was filed by Natco Pharma Limited on 21st July 2007 with a request for hearing under rule 55 of the Patent Rules 2003 as amended by Patents (Amendment) Rules 2005. The applicant accordingly submitted their reply statement and evidence on 21st April 2008. The hearing was fixed on 24th June 2008 and both the parties to the opposition attended the hearing on the scheduled date.

The present application is a Divisional application out of parent application no 920/DEL/1995 (23rd May ,1995) filed by M/s Yeda Research & Development Co ,Israel having priority of USA application dated 23rd November,1994 but in the course of prosecution the applicant dropped the claim to priority of USA. This divisional application was filed on 5th February,2003 for an invention claiming "a co-polymer fraction-1", was allotted the application number 93/DEL/2003.

Opponent in their written statement of opposition not taken any ground of opposition by name available under section 25(1). Opponent has taken grounds as identical product as already in public domain or it is a subject matter of earlier patent or it is non patentable claims. The opposition appears to have been filed by the opponent M/s Natco Pharma Chemicals Ltd. by a person not very much conversant with the legal procedure for writing a written statement of opposition. Nevertheless opposition once filed has to be considered and to be decided. Therefore I shall take those portion of the submission which are allowed under section 25(1) and ignore all the other grounds which are beyond the scope of section 25(1) of the Patent Amendment)Act 2005.

It is evident that the opponents intended to oppose the application on the novelty ground especially the selection of the copolymer fraction , the lack of inventive ingenuity and in terms of therapeutic efficacy under section 3(d). During hearing opponent did not press for the cited document vide annexure 2,5 and 6 in argument & therefore these documents are not taken on record.

Now I shall deal with arguments submitted and made during the hearing by the opponent and countered by applicant. Opponent submitted that the copolymer-1 with the exact amino acid composition & mole ratio (alanine/glutamic acid/lysine /tyrosine as 6:2:5:1) as claimed in the present invention is already described and published in 1971 vide European Journal. Immunol, 1971,1;242-248 (vide annexure 3). The same product has been patented as US 3849550 (Nov 19,1974) with the title “Therapeutic copolymer “ having the same composition mentioned above. On page 3 of the present application it has mentioned that the product of the present invention can be prepared by known methods in the art for example process disclosed in the US Patent 3849550, wherein “N-Carboxyanhydride of tyrosine, alanine, γ -benzyl glutamate and δ -m-trifluoro acetyl lysine are polymerized at ambient temperature in anhydrous dioxane with dimethyl amine as initiator. The deblocking of the y-carboxylic group of the glutamic acid is effected by HBr in glacial acetic acid and is followed by the removal of trifluoro-accelyte group from the lysine residue by 1M Pyridine. The copolymer-1 with the required molecular weight profile can be obtained by method known per se such as chromatography for collecting the fractions without the undesired species or by partial acid or enzymatic hydrolysis to remove the high molecular weight species with subsequent purification by dialysis or ultra filtration. This method was also disclosed in the EU. J. Immunol, publication in 1971 vide (Annexure 3, & Section 2.3.1; page 243 of the document).

Therefore the present invention is the same product having same composition & prepared by the known process and purified by known

means and therefore the product is anticipated by prior publication. The only contribution apparently is the manipulation of the molecular weight of the copolymer-1. In the present invention vide example 2, two batches of copolymer-1 with average molecular weight of 7.3 and 8.4 kDa were prepared along with a copolymer-1 having average molecular weight 22kDa for demonstrating the toxicity test. The opponent argued that the copolymer-1 with average molecular weight of 7.3 & 8.4 kDa were designated as non-toxic and the copolymer –1 batch with average molecular weight of 22kDa was designated toxic, as three out of five mice had died at the end of 48 hours. The veracity of the statement become seriously questionable, on the basis of the clinical trial data reported in “New England Journal of Medicine” of 1987 vide annexure 7, being a publication authored jointly by about fourteen experts .It is reported there that copolymer-1 with molecular weight between 14 kDa to 23kDa was found to be non-toxic during short term and long term administration in mice, rabbit and dogs. The opponent emphasized that it is surprising that the applicant reports the copolymer of 22kDa to be toxic material as three out of five mice dies within 48 hours while the expert report on the clinical trial data vide annexure 7, (New England Journal of Medicien, 1987) where the same species of animal were exposed to a long term administration up to six months were found to be non-toxic. The applicant in their reply dealt with the annexure 7 did not provide any satisfactory or sound argument with respect to the serious discrepancy pointed out and the applicant only tried to conclude that the data referring to 60% death of mice showed that the material would have toxicity in humans although it may not cause death. This reply is not satisfactory to the discrepancy raised with respect to annexure 7. The applicant ought to have brought forward all the evidence of experiment, but it choose not to do so. The annexure 3, teaches that the copolymer-1 with average molecular weight of 23 kDa showed a marked suppressive effect on the disease. The annexure 3 shows vide table 1, batch 1 copolymer of

molecular weight 23 kDa ,reported positive results in diverse studies on animal vide page 248, para 4 in the left hand column.

Opponent argued that the applicant has submitted on page 2 that the alleged invention is directed at modification of molecular weight. The broadest aspect of the present invention is to a copolymer which excludes the species of copolymer-1 having molecular weight of over 40 kDa. The amended claim 1, claims an improved copolymer-1 containing less than 5% of polypeptide species having a molecular weight of over 40kDa and wherein over 75% of polypeptide species of the said copolymer-1 is within a molecular weight range from 2 kDa to 20 kDa and balance 20% being in the range of 21 to 40 kDa which indicates that the copolymer-1 substantially lies within the same range of molecular weight of the copolymer-1 of the prior art.

Opponent further argued that the two prior art documents firstly , i.e. "New England, J. Med.1987, 317:408-414 vide annexure 7 which relates to a copolymer-1 product of molecular weight 14-23 kDa and being non toxic drug exposed to short term & long term administration in mice, rabbits & dogs , which the applicant had acknowledged in the specification. The opponent relied upon second document EP-383620 which discloses that the product of molecular weight in the range of 5-50 kDa synthesized by polymerizing alanine, glutamic acid, lysine and tyrosine or tryptophan . This prior art teaches that copolymer-1 comprises random amino acid sequences mixture, which is non-uniform with respect to amino acid and having average molecular weight 23 kDa.

Combining the teaching of these two citations a person skilled in the art would obviously be motivated to further reduce the molecular weight of the copolymer-1 to reduce further toxicity. The prior art mentioned that the best results have been found for copolymer of 23 kDa or lower range preferably 14 to 23 kDa. Therefore it would be obvious for a person skilled in the art to further decrease the molecular weight copolymer-1, than known in the art with reduced toxicity.

The opponent submitted that applicant attempts to create monopoly in copolymer-1 being a known substance in respect of molecular weight range that is already known and published much prior to the priority date of the opposed application. The only plea of the invention in the use of the lower molecular weight ranges material for lower toxicity , although the example and the data provided do not go to substantiate such a claim on the basis of well established findings of prior art vis-à-vis much higher molecular weight range of 14-23 kDa. Therefore, opponent argued, that it seems to be merely an obvious selection of narrower range of molecular weight being an attempt to provide lower average molecular weight than known in the art. Neither experimental data is found in the alleged invention nor provided subsequently which could have supported the claim of the applicant that copolymer-1 of 4 to 8.6 kDa , is having higher efficacy in treating multiple sclerosis as compared to prior art.

The opponent argued that there exist a linier proportional relationship between toxicity & molecular weight of the product, thus higher molecular weight product is more toxic and low molecular weight product as claimed in the invention is less toxic. Therefore the unexpected result in the alleged invention in view of the disclosure in New Eng.J.Med.1987, 317; 408-414 is not established. The applicant drew a relationship between molecular weight and toxicity but it is completely silent as to the comparative therapeutic benefit of copolymer-1 having molecular weight in the range of 4-8.6 kDa and in absence of such data , no inventive step can be established.

Opponent further argued that on page 2 of the specification of the present invention , it has been mentioned that the invention, resides in a composition of copolymer-1 substantially free from species of copolymer-1 having molecular weight over 40 kDa. This stretched range of molecular weight upto 40 kDa ,the applicant is claiming while the copolymer-1 of the prior art EPO 383620 provides for copolymer -1 having molecular weight upto 50 kDa & further the applicant claims that 75% of the fraction of

copolymer-1 lies within of molecular weight range of 2 kDa to 20 kDa which is very much motivated from the cited document which reports copolymer-1 in the range of 20 kDa.

The opponent further argued that the example 1 prepares two batches of copolymer-1 by conventional method, one batch is subjected to chromatographic separation and a fraction collected as batch A contains 2.5% of the species of copolymer 1 having a molecular weight of more than 32kDa, while in the other batch without subjecting chromatography contains 2.5% of the species has molecular weight of above 42 kDa and 5% of the total copolymer 1 species had molecular weight of over 40 kDa. Therefore the paragraph 3 & 4 of the example-1 are inconsistent with amended claim 1. The in vivo study vide example 2 of the present invention shows that the batches with the average molecular weight of 7.3.& 8.4. kDa are both designated non-toxic whereas, the batch with average molecular weight of 22 kDa is designated as 'toxic' . The result is supported & motivated from the teaching of New EnglJ.Med. 1987,317:408-414 which relates to the copolymer-1 product of molecular weight 14000 Da-23000 Da has been found to be non-toxic during short term and long term administration in mice, rabbits & dogs. Further, the separation of low molecular weight fraction using chromatographic fractionation of copolymer-1 for collecting specific fraction of purified low molecular weight product as preferred in the present invention is a well known commonly practiced process devoid of inventive step.

The opponent further stated that the said invention also lack inventive step because the paragraph 2 of page 4 of present specification provided that the copolymer-1 is administered at a dosage of 20 mg while the administration of 20mg of copolymer-1 is known from the prior art i.e. The New Eng. J.Med. 1987. There is no change or improvement in the dosage, therefore amended claims suffers from lack of inventiveness or obviousness.

The opponent also argued under section 3(d) and stated that the alleged invention describe a copolymer-1 as a purified form of myelin basic protein being a mixture of polypeptides composed of glutamic acid , lysine, alanine & tyrosine in the ratio 6:2:5:1 which is known in the prior art and the invention does not provide any data to substantiate the enhancement in the known efficacy of the copolymer-1 for treatment of multiple sclerosis. The law specifically bar the patentability of such “Pure form” of a known substance that does not result in enhancement of known efficacy of the substance as claimed in the alleged invention and therefore the product copolymer-1 clearly falls with in the scope of section 3(d) of the Patent Act.

The applicant on their part refuted all the allegation of the opponent raised on the grounds of novelty , selection patent, obviousness and under section 3(d). The applicant argued that the prior art copolymer-1 include a mixture of polypeptide that is non uniform with respect to molecular weight and sequence contains a ratio of alamine:glutamic acid :lysine :tyrosine of approximately 6:2:5:1 and it is not generally associated with any specific average molecular weight. The principal difference between the copolymer of prior art to the present invention copolymer-1 is a composition with a lower average molecular weight containing reduced number of high molecular weight species. The claimed composition are superior in providing reduced toxicity. The opponent has failed to appreciate that having similar ratio of amino acids in two composition does not make the same polymer. It is the size of the polypeptides in the composition which characterizes the composition.

The applicant argued , the assertion of the opponent “ that the process for preparing the claimed composition were known in the art and skilled artisan would have known how to reduce the prior art copolymer-1 composition” , is wrong because the time & temperature parameters necessary for achieving the claimed composition were not known at the time of invention and also at the time of invention no one knew what modification

to the prior art would bring about the improvements demonstrated by the claimed invention.

The applicant also refuted the argument of the opponent that the molecular weight of a copolymer product is an inherent property & can not be a subject of a claim. Copolymer-1 is a mixture of different polymers, as the molecular weight of each polymer can vary from batch to batch, the average molecular weight of entire mixture does vary from batch to batch. Despite these variation in batch each batch can retain its identity as copolymer-1. Also the average molecular weight of copolymer-1 can be modified by removing the high molecular weight species, thereby lowering the average molecular weight of the copolymer composition.

Against the ground of inventive step argued ,during the hearing by the opponent, the applicant did not give a satisfactory reply except the point that copolymer-1 of the prior art has higher toxicity. The applicant argued that the objective of the present invention was to prepare lower average molecular weight copolymer-1 having lower toxicity. The applicant found the claimed copolymer having molecular weight distribution as in the present invention claimed not only efficacious but also surprisingly of reduced toxicity compared to the higher molecular weight products.

The argument of the present invention to be a selection invention was refuted by the applicant and said since the present invention is not a selection invention but a product of copolymer species of modified low average molecular weight product. Therefore the reference to EP Board citation T 0666/sq does not have any relevance to the present invention.

Oposing the argument of the opponent that “the reduction in toxicity is only a condition of the product being used in mammal may not be a sufficient criteria for increase efficacy of the copolymer-1 “ the applicant replied that in written submission opponent has based his argument in respect of process only & not in respect of product. Therefore the objection under section 3(d) in respect of product should not be allowed at this stage of hearing proceedings. However, the section 3(d) is not applicable to the

product of the present invention as the product is not new form of a known substance. It is a different composition with different properties compared to the prior art. It does not fall under section 3(d) such as purified form, polymorphic form etc . However the test results provided in the specification are sufficient to establish the enhanced efficacy of the copolymer-1 of the present invention as compared to the prior art composition. Therefore the argument that the present invention falls within section 3(d) , is not proved.

Opponent filed a replication , after the reply statement was submitted by the applicant and stated that said replication was necessary due to the applicant's repeated assertion that the present application relates to a composition with a lower molecular weight and size of the polypeptide in the composition is a critical characteristic of the claimed composition. Though under section 25(1) once opponent submitted their representation of opposition by way of written submission and the applicant has submitted their reply statement there is no provision in the section 25(1) of the Act or rule 55 about taking any other submission on record. However in the interest of justice I have allowed the replication document to be recited upon by the opponent and applicant was given the opportunity to reply on the replication while submitting the written argument by the applicant.

Now coming back to replication to the reply, the opponent argued that applicant asserts that the applicants copolymer-1 is a composition of low average molecular weight and the size of the polypeptide in the composition is the critical characteristic of the composition. From the amended claims 1 to 5 it is evident that the reply statement of the applicant, that copolymer-1 has a lower average molecular weight of preferably 4 to 9 kDa ,is a critical aspect of the alleged invention. The opponent argued that the prior art EP 0383620 discusses a procedure for synthesizing gene encoding polypeptides composed of specific amino acid but having random amino acid sequence. The preamble of the amended claims recites the claimed polypeptide as being non-uniform with respect to molecular weight

and amino acid sequence. The said document further teaches that the size of the polypeptide is controlled by synthesizing genes of specific length.

On page 2 and page 50 of the said document provide the synthesis of polypeptide similar to copolymer-1 and example of the said procedure is disclosed therein. On page 3, line 14-16, teach that a preferred copolymer consist of glutamic acid (G) lysine(L), alanine (A) & tyrosine (T) (which are also the constituents of GLATramer is copolymer-1 of the present invention) and have a molecular weight of about 5000 to 50,000 Da. On page 5, of the same document teaches that synthetic genes of 400-600 nucleotide encode polypeptides of 15,000 to 23,000 Da. Example 41 to the said document '620 teaches the strategy of synthesis of random sequence genes. These genes were analyzed for size (i.e. length), legation junction, composition, sequence and level of expression as copolymer-1 containing fusion polypeptide. Following those analysis genes of the following three sizes been isolated i.e. 75-150, 280-320, 400-600 nucleotide.

The opponent argued that by simple principle of unitary mathematics reveal the molecular weight of the resulting polypeptide encoded by genes having nucleotide having these size ranges as follows.

(1) Gene nucleotide size (length) of 75 to 150 nucleotide will correspond to a polypeptide of molecular weight 2842 to 5685, gene of the size of 280-320 nucleotide will correspond to polypeptide to having molecular weight 10612 to 12128 Da and gene of the size of 400-600 nucleotide will correspond to a polypeptide having molecular weight 15000 to 23,000 Da.

The opponent argued that this document therefore provide a method for preparing copolymer-1 of low, intermediate and higher average molecular weight ranges. And the low molecular weight copolymer-1 precisely corresponds to the copolymer-1, molecular weight being claimed in the impugned application. The opponent stressed that it is a well settled principle of patent law that a prior art disclosure is considered as novelty

destroying of the claimed subject matter and can be inferred directly & unequivocally from the disclosure including the feature which for a skilled person are implicit in what is explicitly disclosed.

Applicant in reply to this replication argument of the opponent, argued that EP '620 discloses a synthetic process for preparing polypeptide of a uniform molecular weight and sequence. The applicant referred to the paragraph 4 of EP '620 ----“ a polypeptide produced by a particular colony has a somewhat random amino acid sequence, but all of the polypeptide made by the colony have the identical sequence of amino acid & therefore all such polypeptide have identical molecular weight.” In contrast the present invention provide copolymer-1 having polypeptide that are non-uniform with respect to amino acid sequence and molecular weight i.e. each polypeptide in the mixture of copolymer-1 has different sequence & molecular weight. Therefore the EP'620 does not anticipate the present invention because of the vast difference in the polypeptide sequence.

Now after hearing both the parties I shall analyse the argument, citation etc. to reach to my considered opinion. First of all I shall first deal with the replication petition which was taken on record in the interest of justice . On closely analyzing the prior art EPO 383620 , I find that EP'620 provides a method for making a synthetic gene encoding a random polymers of amino acid which has predetermined amino acid constituents & comprises the polymerization of small oligonucleotides duplexes. The process of the invention here, is unique in that random-sequence genes are synthesized using oligonucleotide duplexes encoding small segments of amino acid and the sticky ends on each duplex are the same. Whereas the copolymer-1 of the present invention is a mixture of polypeptides composed of same four amino acids but it is synthesized by chemically polymerizing the four amino acid forming a mixture of polypeptide. The resulting polypeptide's are comprised of the same amino acid component but they differ with respect to their amino acid sequence. Therefore the EP'620 document does not at all anticipate the present invention.

Here it is pertinent to refer that since the opponent replication was taken on record, in the interest of justice, the applicant were given additional time & opportunity to reply to replication petition which was submitted by the applicant after two months of the submission of written argument. Since I have rejected the citation taken up by the opponent in the replication petition, the counter argument placed by the applicant become infractions and therefore those arguments were not referred unnecessarily.

In respect of anticipation the opponent pleaded that the present invention is a selection as the product claimed by the applicant is substantially covered by prior art. The opponent argued that vide citation of a EPO Board in case No. T 0666/89, "*Patents are not granted for the sole reason that they are selection, but only for new & inventive subject matter of certain defined kinds*" and the applicant in this case does not claim it to be a selection because it can not justify the requirement of selection as well as is unable to show any benefit for such reduction in the average molecular weight than the prior art.

Even if I agree with the opponent argument that the present invention being a selection over the prior art copolymer composition and in spite of the fact that inherency of anticipation is always presumed in that selection unless such presumption is rebutted by proving that the prior art product does not possess the characteristic of the present invention. Now it is to be examined whether in the present invention , the different fraction comprised in the copolymer-1 composition is different than the prior art copolymer composition. The present invention composition comprised a major fraction of more than 75% of polypeptide chain having molecular weight 2 to 20 kDa and only 5% or less of the total composition is having polypeptide chain corresponding to more than 40 kDa. Whereas the prior art polymer composition comprised of fraction having average molecular weight of 23kDa. The amino acid composition/ mole ratio being alanine/gulatic Acid/ lysine/tyrosine as 6:2:5:1 are same in present invention as well as in

the prior art. Therefore the only difference in the present invention is that ,the large part of its composition, ie about 75% or above is comprised of polypeptide chain of molecular weight ranging between 2-20 kDa. I am of the opinion that the composition of polymer fraction in terms of molecular weight and its distribution in the present invention is different from the fractions composed in the composition of prior art. Therefore the present inventor of composition of copolymer-1 is novel over the composition of prior art.

Now whether the modified composition or the composition manipulated from the prior art copolymer is a non-obvious variation from the prior art and if so whether such variation has led to solution to a problem or whether such variation resulted into enhancement in the efficacy of the resulting product with respect to the prior art ?

For finding out the inventiveness , following observation, taken from prior art citations and the arguments / evidence given by the parties to the opposition, need to be analyzed.

- (1) Copolymer-1 is a potential therapeutic agent for multiple sclerosis recognized since 1950, and in the present invention it is for the same purpose only. The applicant has modified / isolated from the prior art copolymer-1 which is first prepared by the identical process prescribed in the prior art. The approach broadly is to modify the copolymer to obtain a improved copolymer-1 which is substantially free from species of copolymer-1 having molecular weight over 40 kDa and to have more than 75% of the copolymer-1 having molar fraction within molecular weight range 2 kDa to 20 kDa, more preferably 4 to 8 .4 kDa
- (2) The improved copolymer-1 of the present invention are prepared by known method per se, such method include chromatography or partial acid or enzymatic hydrolysis followed by dialysis or ultra filtration vide specification page no 3 para 4. The applicant

contribution lies in the manipulation of the prior art product to modify & isolate the narrower average molecular weight species of the prior art copolymer-1.

- (3) The specification demonstrated that batches with average molecular weight 7.8 & 8.4 kDa were found to be non-toxic and a batch having average molecular weight of 22kDa was shown to be toxic as three out of 5 mice died at the end of 48hrs.
- (4) A clinical trial data reported in “ New England Journal of Medicine” of 1987, a publication which was authored by fourteen experts, reported that copolymer-1 with molecular weight 14 kDa to 23 kDa was found to be non-toxic during short term and long term administration in mice, rabbits & dogs. The applicant argued that these inferences are merely a communication without any substantiation by data. I agree with their point that no data was provided in this reference but the pilot trial was conducted on human patient which must have been preceded by the trial on animal and only on the encouraging report, this trial was undertaken for finding out the effect of copolymer –1 in exacerbating-remitting multiple sclerosis.
- (5) The above journal on the concluding part ,clearly indicates “The result show that copolymer-1 administered subcutaneously for two years at a daily dose of 20 mg produced clinically important and statistically significant beneficial effect.....” It also mentioned that “as compared to Placebo certain undesirable side effects were observed , primarily local irritation at injection sites and rare transient vasomotor response, – were well tolerated”. This clearly indicated certain minor disadvantage in the form of side effect in the long term administration of the copolymer-1 of the prior art, observed way back in 1987.
- (6) The present invention provided that the copolymer batch with average molecular weight of 22kDa, 3 out of 5 mice died at the

end of 48hrs. Whereas batches with average molecular weight of 7.3 & 8.4. kDa , no adverse sign was observed. Therefore copolymer batch with average molecular weight 22kDa was designated as toxic. In contrast to this the Eur.J.Immunol. 1971, page 242-248, 'Suppression of experimental allergic encephalomyelitis by synthetic polypeptide's conducted trial with copolymer-1 with average molecular weight of 23kDa showed a marked suppressive effect on the disease. In the document the copolymer-1 with an average molecular weight of 23kDa shows a positive result on animal.

- (7) The prior art EP 0383620 reports copolymer-1 of molecular weight 5-50 kDa which process is a synthetic process of preparing a polypeptide chain of uniform molecular weight and sequence, i.e. all the polypeptide made by the colony have the identical sequence of amino acid and therefore all such polypeptides have identical molecular weight. In this they have taken a size selection of legation product by selecting the region corresponding to the desired size range of 400-600 nucleotides, synthetic genes of 400-600 nucleotides encodes polypeptide of 15000-23000 Daltons. It mentioned that ***“we have selected genes of approximately this size because copolymer-1 polypeptide of 15000-23000 range were previously tested in chemical trial “*** & the same document further on testing have shown that ***” the copolymer-1 of 15-23 kDa size were effective in suppressing experimental allergic encephalomyelitis (EAE). Clearly indicated that the lower size polypeptide i.e. 15-23 kDa was showing better result in chemical trials.***

From the above 7 points one can summarize (a) that copolymer-1 of the prior art as well as of the present invention is a potential therapeutic agent for multiple sclerosis & known for long. (b)The applicant in the present invention has modified/ isolated the

prior art copolymer-1 by known method like chromatography, acid/enzymatic hydrolysis etc. to obtain a lower average molecular weight copolymer-1 species particularly in the range of 2-20 kDa with no more than 5% species having molecular weight above 40 kDa.

©The selection of lower average molecular weight copolymer-1 was motivated from three citations. One is new Eng. Med. 1987 (P-317,408-414) Annexure-7 wherein it was mentioned that copolymer-1 product having average molecular weight 14 kDa to 23 kDa which was found to be non-toxic during short term & long term administration in mice, rabbit and dogs, The second citation is Ear.J. Immunol, 1971,242-248 vide Annexure 3, shows different composition of copolymer and in Table 1 one batch of copolymer-1 shown to be of 23.1 KDa average molecular weight and the document specially report positive result in studies on animal vide page 248 of the same document. The third citation is a EP 0383620, wherein synthetic genes of 400-600 nucleotide genes encodes polypeptide of 15-23 KDa because copolymer-1 polypeptide within this range were found to be most appropriate & were subjected to chemical trials (Page 5).

Now combining these three citation , a person skilled in the art would be definitely motivated to further reduce the size of the polypeptide chain length / molecular weight by conventional means, to obtain further reduced average molecular weight copolymer-1 than the prior art copolymer-1. From the prior art citation the average molecular weight of copolymer-1 upto 23kDa was found by trials & experimentation (some of these mentioned above) to be safe & effective by several researcher and further bringing down the average molecular weight or in other words narrower lower range is an obvious exercise for a person skilled in the art.

The applicant's toxicity experiments and analysis are inadequate for reaching a conclusion reasonably. The finding of the New.Eng.J.Medi 1987 vide annexure 7 gives a report in which copolymer-1 of 15-23kDa was found to be safe for short term & long term administration on animals whereas the only one experiment shown in the body of specification, mentioned that 60% of the mice died in 48 hrs. I agree with the opponent's view that the said report is not reliable, further experimental evidence should have been forwarded at least during prosecution, particularly on the face of it being contradictory to the report of annexure 7 as well as the inferences shown in Annexure 3 and prior art EP/0383620 specification of copolymer-1. Even if it is so, the present application in its claim provided, 25% or more of the fraction of copolymer-1 of the present invention which might be falling above 22 kDa which was shown to be highly toxic yet included in such high proportion in claim 1. This again clearly justifies the prior art citation annexure 7 that upto 23 kDa average molecular weight copolymer-1 is safe and effective for long term administration & it is the main motivating factor for the skilled person in the art to further reduce the average molecular weight. I therefore do not find the selection of copolymer-1 having 75% or more consist of 2-20 kDa including the preferred aspect of 4-8.4KDa average molecular weight with less than 5% above 40 kDa from the prior art copolymer-1 to be non-obvious & inventive. The application fails to clear the ground of obviousness & lack of inventiveness.

The present invention is nothing but a modified copolymer-1 of the prior art copolymer-1 with narrower molecular weight distribution specifically of lower molecular weight species. All the fraction of different molecular weight species isolated are comprised in the prior art copolymer-1 composition although in differing proportions, In my opinion the applicant's argument that it is a different composition with different properties and it is not a selection is not a very correct and

logical argument. The present invention is definitely a selection from the prior art, all the species present in the present invention is also comprised in the prior art composition & is a subject of section 3(d) being a product, made up of component species. Therefore objections raised by the opponent under section 3(d) is arguable. Every selection will lack in inventiveness if it is not accompanied by surprising efficacious effect. The specification of the present invention does not provide any data to substantiate any enhancement of known efficacy of the copolymer-1 which is a narrower molecular weight distribution composition having lower average molecular weight than the prior art composition or in other words the selected species of low average molecular weight from the broad molecular weight distribution copolymer-1 of prior art by known method , does not show any enhancement in the known therapeutic efficacy other than it being less toxic to animal comparatively. Neither in the specification any data is provided to show the efficacy enhancement compared to prior art nor any document submitted for evidence of experimental data during the prosecution of the opposition proceedings. The toxicity analysis appears to be inadequate and applicant ought to have forwarded more evidences of its experiments. Therefore under section 3(d) of the Indian Patent Act which takes cognizance of such modification under this section , is not satisfied or in other word the requirement of this section not fulfilled. The application fails to qualify the section 3(d) of the Indian Patent Act.

As the invention claimed in the present invention is an obvious modification of prior art copolymer-1 and does not involve and inventive step over the disclosure in the prior art vide annexure 7, therefore the claimed invention is not an invention within the meaning of section 2[1(j)] of the Patent Act 1970.

In view of my finding in the preceding paragraphs, I conclude that the present invention as claimed in revised claim 1 to 8 of the application number 93/del/2003 is ;

- (a) obvious and does not involve an inventive step over the prior art.
- (b) Not an invention within the meaning of the section 2[1(j)] of the Patent Act 1970.
- (c) Not patentable invention within the meaning of section 3(d) of the Patent Act 1970.

On the basis of the above findings and the circumstances of the case, I refuse to proceed with the application number 93/del/2003 for grant of patent.

The application stand disposed off with no cost to either party

Dated this, the day

(S. K. ROY)
Asstt. Controller of Patents & Designs.
IPO, NEW DELHI.

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