IPAB Intellectual Property Appellate Board

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Dated : 2ND November, 2012

OA/8/2009/PT/CH & M.P.NO.85 & 111/20012 IN OA/8/2009/PT/CH
Arising out of Order-in-Original dated 17.3.2009 and passed by Assistant Controller of Patents and & Designs in respect of Patent Application No.1032/MAS/1997.

8647

Between

APPLICANT / APPELLANT	**REPRESENTATIVE**
SANKALP REHALIBITATION TRUST, 115B BELLE VUE, DR. AMBEDKAR ROAD, MUMBAI 400 050	MS. R. VAIGAI, NO:2, IST FLOOR, S.M. PLAZA, 45, ARMENIAN STREET, CHENNAI 600 001.
	Vs.
RESPONDENT	**REPRESENTATIVE**
1) F.HOFFMANN-LA-ROCHE AG, A COMPANY ORGANISED UNDER THE LAWS OF SWITZERLAND OF 124, GRENZACHERSTRASSE, CH-4070, BASEL, SWITZERLAND. **Address for service in India :** DE PENNING & DE PENNING, 120, VELACHERY MAIN ROAD, GUINDY, CHENNAI 600 028.	DE PENNING & DE PENNING, 120, VELACHERY MAIN ROAD, GUINDY, CHENNAI 600 028.
2) ASST. CONTROLLER OF PATENTS & DESIGNS, IPR BUILDING, G.S.T. ROAD, GUINDY, CHENNAI 600 032.	

I am directed to send herewith the certified copy of the **Order No.250/2012** passed by the Hon'ble Board on 2ND November, 2012 in respect of **OA/8/2009/PT/CH.**

(N. ANBAZHAGAN)
DEPUTY REGISTRAR

Copy forwarded to:

1)	MS. R. VAIGAI,NO:2, IST FLOOR, S.M. PLAZA, 45, ARMENIAN STREET, CHENNAI 600 001.
2)	DE PENNING & DE PENNING, I20, VELACHERY MAIN ROAD, GUINDY, CHENNAI 600 028.
3)	ASST. CONTROLLER OF PATENTS & DESIGNS, IPR BUILDING, G.S.T. ROAD, GUINDY, CHENNAI 600 032.
5)	PTC (by email)
6)	MANUPATRA INFORMATION SOLUTIONS PVT. LTD, 16A, 2ND FLOOR, WELLINGDON ESTATE, 24, ETHIRAJ SALAI, CHENNAI-600 105 (by email)
7)	GUARD FILE
8)	A. VAIDYANATHAN, STENO 'C' = FOR UPLOADING THE ORDER IN THE IPAB WEBSITE IMMEDIATELY.

INTELLECTUAL PROPERTY APPELLATE BOARD

Guna Complex Annexe-I, 2nd Floor, 443 Anna Salai, Teynampet, Chennai-600018

OA/8/2009/PT/CH
and
M.P. NOs.85 & 111 of 2012
In
OA/8/2009/PT/CH

FRIDAY, THIS THE 2ND DAY OF NOVEMBER, 2012

HON'BLE SMT. JUSTICE PRABHA SRIDEVAN ... CHAIRMAN
HON'BLE SHRI D.P.S. PARMAR ... TECHNICAL MEMBER (PATENTS)

Sankalp Rehabilitation Trust,
115-B, Belle Vue,
Dr.Ambedkar Road,
Mumbai 400 050.

... Appellant

(Represented by Advocates: Mr.Anand Grover, Sr.Counsel for
Ms.R.Vaigai, Ms.Anna Mathew, Ms.S.Prathiba & Ms.Sumathi)

Vs.

1. F.HOFFMANN-LA ROCHE AG,
   A company organized under the laws of
   Switzerland of 124, Grenzacherstrasse,
   CH-4070, Basel, Switzerland.

2. The Asst. Controller of Patents & Designs,
   IPR Building, GST Road, Guindy,
   Chennai9 600 032.

...Respondents

(Represented by Advocate: Mr. Rahul Balaji, Mr. Arunava Mukerjee for
M/s.Depenning & Depenning and Mr.D.J.Solomon, Regd. Patent Agent - for R1)

ORDER (No. 250/2012)

Hon'ble Smt. Justice Prabha Sridevan, Chairman.

Two post-grant oppositions were filed against the grant of Patent No.198952 [Application No.1032/MAS/1997] titled, "A physiologically active branched PEG-IFN alpha conjugates". The invention is a medicine for Hepatitis-C, an emerging disease in India. Both were disallowed. One

of them was a business competitor of the patentee and it accepted the rejection. The other is the NGO, who is the appellant before us.

2. The patent applicant claimed priority from its U.S. application dated 31.5.1996. It was published in the journal on 19.5.2006. M/s.WOCKHARDT Ltd. filed a notice of opposition, who was the first opponent. The appellant herein filed another notice of opposition on 18.5.2007 and an Opposition Board was constituted. The Opposition Board gave its recommendations on each of the oppositions. With regard to the M/s.WOCKHARDT opposition, the Opposition Board recommended that the invention lacked novelty and inventive steps, "keeping in view of R3 to R6". As regards the opposition filed by the appellant/2nd opponent, the Opposition Board held that there is novelty, but there is no inventive step and the invention does not fall under section 3(e) of the Patents Act, 1970, but falls within the scope of section 3(d). The Assistant Controller decided both the opposition proceedings on the same day but, dealt with each opposition separately and did not agree with the recommendations of the Opposition Board and concluded that the First Opposition did not merit acceptance and that the patent was novel and had inventive steps. As regards the appellant's opposition, the impugned order concluded that the claims were novel and had "inventive step" and also industrial applicability and that the claims do not attract the provisions of section 3(e) of the Act. He opined that "even if any person feels that the claims attract the provisions of section 3(d), the experimental details as provided by the patentee prove that there is indeed an enhancement in known efficacy of either unconjugated interferon or PEG interferon α 2b (12KD)

and probably with other conjugates of lower MW." This appeal challenges those findings.

3. Mr.Anand Grover, Senior Counsel instructed by Ms.Julie George and Ms.Prathiba S. appeared for the appellant, Mr.Rahul Balaji learned Counsel and Mr. D.J.Solomon registered Patent Agent appeared for the respondent. They argued the matter and also filed written submissions.

4. The first respondent raised a preliminary objection regarding the locus standi of the appellant as not being a 'person interested' and submitted that the difference between the words, 'any person' used in S.25 (1) of the Patents Act, 1970 ('The Act', in short) i.e.the pre-grant opposition and 'any person interested' inS.25 (2) of the Act i.e. the post-grant opposition cannot be ignored. Mr.Rahul Balaji, the learned counsel submitted that the 'person interested' may be a person in business or a person who may be a potential infringer who has research facility. But, to allow 'any person' to file the post-grant opposition would render the difference between the two terminologies as non-est. He referred to the words used in the Land Acquisition Act, 1894, and he submitted that the language intends to exclude a mere busybody. He submitted that the legislative history of S.25 would throw light in this regard. There was no post-grant opposition prior to the Patents (Amendment) Act, 2005 and specifically the Parliament has introduced the words 'person interested' for maintaining a post-grant opposition. Learned counsel referred to the observations of the Hon'ble Delhi High Court in UCB Farchim CA v. Cipla Ltd. & Ors. [2010 (42) PTC 425 (Del.)] where the difference between the

pre-grant and post-grant oppositions was noted and it was observed that "the legislature appears to have consciously denied to a third party a further statutory remedy of a post-grant opposition in the event of such third party not succeeding in the pre-grant stage". Learned counsel referred to the definition of 'person interested' in S.2 (1) (t) of the Act and relied on several decisions to explain who is a 'person interested'. He referred to Globe Industries Corporation's Patent [1977 RPC 563] where the U.K. Court of Appeal held that not only should the interest be a commercial interest, it must be a genuine interest and there must be an existence of real prejudice and that the Court must be satisfied that the opposition is not frivolous, vexatious or a piece of blackmail. Learned counsel submitted that at the very least there must be a genuine commercial interest and therefore, the appellant who claims to be a non-profitable organization working for the benefit of drug users cannot be said to have any interest of the nature as required by the Act. Learned counsel also submitted that the appellant cannot take advantage of the word, 'include' in the definition section. He submitted that the Court must see the context to understand what the word 'include' means and referred to the judgment of the Hon'ble Supreme Court in Reserve Bank of India v. Peerless General Finance and Investment Co. Ltd. [(1987) 1 SCC 424] where the Supreme Court held that that the best interpretation is the one which makes the textual interpretation match the contextual. Therefore, according to the learned counsel for the respondent, a person engaged in or promoting research in the same field, but lacking commercial interest may not be otherwise understood as coming within the ambit of 'person interested'. Learned counsel referred to Inspecting Assistant

Commissioner, Acquisition Range v. Nand Kishore Singh & Ors. [1984 (148) ITR 721] where in the context of Income-tax Act, the Hon'ble Patna High Court held that the words 'person aggrieved' is of wider amplitude than the term 'person interested' and the 'person interested' necessarily entailed the existence of a stake in the subject of the proceedings. Therefore, it was submitted that reliance must not be placed on Ajay Industrial Corpn. V. Shiro Kanao [AIR 1983 Delhi 496] where the Hon'ble Delhi High Court observed that the word 'person interested' in the Patents Act is perhaps wide than the 'person aggrieved' under the Trademarks Act. Learned counsel submitted that while in a pre-grant opposition any person including an NGO can maintain the opposition, the right is restricted to a 'person interested' in a post-grant opposition. He referred to Snehlata C. Gupte v. Union of India & Ors. [2010 (43) PTC 813 (Del.)]. A wide interpretation to the words 'person interested' would mean that any person/entity making a very broad claim of acting in the arena of public health would be entitled to maintain a post-grant opposition. Only a person with a real, tangible and clearly perceived interest in the patent can maintain the opposition. Learned counsel submitted that there are several sections to use the words, 'person interested' in the Act viz., Ss 25(2), 57(4), 61(1), 63(3), 78, 84, 85, 92 and it would be incongruous to assign a broad meaning considering the context in which the term was used in the above sections. Learned counsel submitted that the consideration of public interest as being an important factor cannot be accepted because, there are several safeguards inbuilt in the Patents Act especially, with regard to the access to pharmaceutical inventions which included procedure for voluntary license, compulsory license and the Government's

ability to take over a patent under S.100 and S.47 in the larger public interest. Learned counsel submitted that therefore the appellant not being a person interested cannot be allowed to maintain the appeal. He also prayed that an order may be passed on the jurisdictional issue without going into the merits for, the appellant is not a 'person interested' and it is not necessary for this Board to engage itself to deal with the issues on merits

5. Mr.Anand Grover the learned senior counsel for the appellant submitted that the appellant is a community based organization that provides care and treatment for injecting drug users such as, HIV patients and since the patent in question is in respect of a medicine used to cure Hepatitis-C which is prohibitively expensive and out of reach of the community for whom the appellant works, the appellant is definitely a 'person interested'. Learned counsel referred to paragraph-6 of its opposition where it is stated that the opponent being an organization that provides care, support and treatment for injecting drug users many of whom are infected with HCV, is therefore vitally interested in the outcome of the present proceedings. Learned counsel submitted that the word, 'interested' should be construed so as to mean an opponent having interest in the grant of a particular patent and even if the opponent is doing research on the impact of the drug in issue or a beneficiary or a consumer of the medicine, there is definitely an interest in the grant of the patent. Learned counsel submitted that in the entire Patents Act, there is a public interest element and the appellant is interested in the community of people where the interest in the issue is direct. Learned counsel submitted that

the patentee did not raise any objection on the maintainability of the opposition at the earliest stage but, without any demur, had taken part in the hearing and it was only at the time of hearing had raised an objection with regard to the locus of the appellant and because of the belated jurisdictional objection raised, the Controller refused to consider that objection. Learned counsel referred to Remington Rand of India Limited v. Thiru R.Jambulingam [(1975) 3 SCC 254] where it was held that once a party submits to the jurisdiction of a court, it cannot then assail it. It is submitted that it is an established position of law that an inclusive definition is not exhaustive and is prima facie extensive and referred to the decision in West Bengal State Warehousing Corporation v. Indrapuri Studio Private Limited [(2010) 14 SCC 285]. Learned counsel submitted that those affected by the continuation of the patent on the Register are definitely 'persons interested' and referred to Ajay Industrial Corpn. V. Shiro Kanao [AIR 1983 Delhi 496]. He also referred to the observation of the Hon'ble Delhi High Court which equated the expression 'person interested' even to 'a person who pro bono publico initiates a public interest litigation and makes an application to vindicate a legal injury'. According to him, therefore, the appellant raising a public interest on the issue of access to medicine is definitely a 'person interested'. He referred to the decision of the Central Intellectual Property and International Trade Court of Thailand in AIDS Access Foundation and others v. Bristol-Myers Squibb and another (Black Case No.Tor Por 34/2544, Red Case No.Tor Por 93/2545, dated 1.10.2002) where it was held that the expression 'person interested' would include an organization representing persons living with HIV. He referred to the order in Patent Application

No.959/MAS/1995 passed by the Asst. Controller of Patents & Designs, dated 30.4.2010 [M/s.F.Hoffmann-La Roche AG v. M/s.Ranbaxy Laboratories Ltd. and others] which had also dealt with the words 'person interested'. He submitted that the beneficiary is considered to be a 'person interested' in the Land Acquisition matters in Neyveli Lignite Corporation Ltd. V. Special Tahsildar (Land Acquisition) Neyveli and others [(1995) 1 SCC 221]. With this the learned senior counsel prayed that the jurisdiction issue may be held in favour of the appellant.

6. The Patents Act, 1970 defines the words 'person interested' in S.2 (1) (t) and the definition "include a person engaged in or in promoting research in the same field as that to which the invention relates". S.25 (1) which deals with the pre-grant opposition uses the words 'any person'. S.25 (2) deals with post-grant opposition and uses the words 'any person interested'. The grant of a patent does not guarantee the validity of the patent. In Ajay Industrial Corpn. v. Shiro Kanao [AIR 1983 Delhi 496], the Delhi High Court held that

> "In our opinion, a 'person interested' within the meaning of section 64 must be a person who has a direct, present and tangible commercial interest or public interest which is injured or affected by the continuance of the patent on the register".

In the decision of the Central Intellectual Property and International Trade Court of Thailand in AIDS Access Foundation and others v. Bristol-Myers Squibb and another (Black Case No.Tor Por 34/2544, Red Case No.Tor Por 93/2545, dated 1.10.2002) relied on by the appellant, it was held as follows:

> "Therefore, the injured parties from the grant of patent are not limited to the manufacturers or the sellers of medicine protected by the patent. The patients or those in need of the medicine are also interested parties to the grant of the patent."

In Novartis AG and another v. Union of India and others [2007 (4) MLJ 1153], the Hon'ble Madras high Court while dealing with the constitutionality of S. 3(d) referred to "the fear of the common man being denied access to life saving medicines and it would encourage evergreening". The Doha declaration was about public health, the TRIPS flexibilities are taken advantage in terms of public health emergencies and crisis.

7. In fact, in W.B.State Warehousing Corpn. V. Indrapuri Studio (P) Ltd. [(2010) 14 SCC 285] the Supreme Court compared the definition of the 'person interested' in the Land Acquisition Act and also referred to N.D.P. Namboodripad v. Union of India [(2007) 4 SCC 685] where the Supreme Court has held that the word 'include' has different meanings in different contexts. The respondent relied on Northern Plastics Ltd. v. Hindustan Photo Films Mfg. Co.Ltd. [(1997) 4 SCC 452] where it was held that an appeal being a creature of statute only a person permitted by the statute and subject to the statutory conditions can file appeal. In UCB Farchim SA v. Cipla Ltd. & Ors. [2010 (42) PTC 425 (Del.)] the Hon'ble Delhi High Court had noted the difference between the third party viz., "any person" and "a person interested" and held that the legislature appears to have consciously denied to a third party a further statutory

remedy of a post-grant opposition in the event of such third party not succeeding in the pre-grant stage to prevent the grant of patent.

8. The interpretation of the word 'includes' as seen from, W.B.State Ware-Housing Corpn. V. Indrapuri Studio (P) Ltd. [(2010) 14 SCC 285], indicates that prima facie when the definition clause uses the word 'includes', it is used as a word of enlargement that is, to make the definition extensive and not restrictive. It is also submitted on behalf of the respondent that the word must be understood both from textual and from contextual angles. The legislature has undoubtedly used different terminology for the persons who are entitled to bring in an opposition that is, in one case, 'any person' and in the other case, 'any person interested' but, it is clear from the definition clause that there need not be a commercial interest to be a person interested for, otherwise the definition would not have used the words, 'person engaged in or in promoting research in the same field'. The Ajay Industrial Corporation (cited supra) ruling that anyone who is affected or injured by the continuance of the patent is "a person interested" must be applied. In this context, we may also see if there is a presumption of validity of a patent in the Patents Act (Act in short) for that may assist us. The III Schedule, Form of Patent as it originally stood clearly mentioned that the validity of the patent is not guaranteed whereas those words are not found in the present III Schedule, Form of patent. But, we are not sure whether that alone would be sufficient for us to hold that the Act creates a presumption of validity. In fact, by the present Act one more level of opposition has been created by the introduction of post-grant opposition. This is so because at the

application stage, it is possible that the threshold is not high and the law never intended that undeserving monopolies should be created. The filter at the IPO stage may also not be as effective as required. So, to safeguard against this, we have a three-stage challenge, a pre-grant, a post-grant and then, the revocation. And it is at the post-grant stage that the appellant came in.

9. There is no statutory presumption of validity in the Act, as there is in the Trademarks Act where, under S.31 registration is a prima facie evidence of validity. But, there is no similar provision in the Patents Act that the grant is a prima facie evidence of validity. In fact, there is S. 13 (4) which says that the examination and investigations required under Ss12 and 13 shall not be deemed in any way to warrant the validity of the patent. Due to the purely non-adversarial nature of the grant of patent where there is no pre-grant opposition, we cannot exclude the possibility of an unjustifiable invention getting a grant. It is only because the filters may be porous at the IPO, that even after the two tier oppositions, revocation is provided.

10. Even where the same words have been used viz., 'person aggrieved' under Ss 47 and 57 of the Trademarks Act, the Hon'ble Supreme Court in Infosys Technologies Ltd. vs. Jupiter Infosys Ltd. and another [(2011)1 SCC 125] held that the words 'person aggrieved' in S. 57 must be given wider interpretation in view of the public interest. We must adopt the same approach in considering the locus standi of the appellant herein. The continuance of an unworthy patent on the Register is not only

against the interest of other persons carrying on the same business but also against the public interest. For the protection of valid patents, we have no doubt to prevent the busybodies and unnecessary interferences. But, it is as much against the public interest to allow unworthy patents to be on the Register, as it is to prevent third parties having no interest from attacking a deserving patent. While liberally construing the words 'person interested', we could balance the cause of justice by awarding exemplary costs against an opponent who really has no interest in the grant of patent. The interest should not be a fanciful interest. We must take a common sense approach to construe the interest that the opponent has in opposing the grant of a patent. In the present case, the appellant claims that it is a society which works for the community of HCV and HIV sufferers. This is not challenged. The invention is admittedly for the use in the case of hepatitis-C. The continuance or removal of the patent will definitely affect the interest of the community for whom the appellant claims to work. The appellant has challenged the patent on several grounds, if the challenge succeeds, the monopoly will be broken. This is something that the appellant is interested in, since it will bring the drug within the reach of the community for whom it works, not only because of reduction in cost, but also because of increase in supply. When the Act includes" a person doing research" in the definition of person interested, an interest which is an academic one and not necessarily commercial, and when the Act only uses the word "includes" which is a word which is not restrictive, we may correctly apply the Ajay Industrial case and the Thailand Court case. If the law intended that there should be a presumption of validity, it will state it explicitly. We cannot read it in, that

would amount to "legislating." **Further public interest is a persistent presence in intellectual property law and will not melt into thin air, nor dissolve**. We therefore hold that the appellant who works for a community which needs the medicine is definitely a 'person interested" **The locus standi objection is rejected.**

11. The respondent requested that this issue may be dealt with as a preliminary issue. Though we are not bound by the Civil Procedure Code, the CPC provides for dealing with the preliminary issue only as a matter of discretion that too, when the preliminary issue is purely a legal issue. It is better that all the issues both on law and facts are dealt with together to avoid delay in the matter in dispute. The length of intellectual property litigation must be curtailed and if it is legally possible to expedite the matter without sacrificing the cause of justice, that mode should alone be adopted. So, we proceeded to hear them on merits too.

12. The appellant filed **M.P.111/2012** to receive additional evidence. This was opposed by the respondent. At this juncture, we also need to observe that the principles of C.P.C and the decisions given thereon may not always be applicable in a patent or trademark litigation, more particularly in a patent litigation. We may in civil litigation on the particular facts of the case refuse to receive the evidence and documents, if they are belatedly produced before the Court. But it is extremely doubtful, if we can apply the same principle broadly to all the documents that are sought to be produced before us. It may be that the 'person interested' in opposing the grant or interested in revoking the grant had belatedly come

across a prior art which squarely anticipates the patent or renders the patent obvious. The delay may not be wanton or due to lack of diligence. The Controller or the Board cannot shut out the documents merely on the ground of delay. A patent is granted only for an invention, which is a new product or process involving inventive steps and capable of industrial application. The inventive step is defined in S.2 (1) (ja). It could have a feature of an invention which involves technical advances as compared to the existing ones or it may have economic significance or both which makes the invention not obvious. It is an invention which has not been anticipated by a prior publication. S.3 clearly states, what are not inventions. If revocation is filed on one or more of the various grounds spelt out in S.64 which would include novelty, obviousness, lack of inventive steps, etc. and the documents are belatedly produced to support the case, the Controller cannot shut his eyes and allow the patent to remain merely because the documents have been produced belatedly. On the other hand, the Controller has a duty in law to make sure that a patent wrongly granted contrary to the provisions of the Patents Act is revoked. Because, that which ought to be in public domain has wrongfully been granted a monopoly and it is the duty of the Controller to bring it back to the public domain. The law mandates that the Controller revokes the patent which falls foul of S.64. We do not think that the Controller has an option to revoke or not to revoke the patent which is granted to an obvious invention, or an anticipated invention or an invention hit by section 3(d) or 3(k) or a patent which is hit by any of the other grounds in S.64. Once the revoker successfully proves his grounds of revocation, then the patent shall be withdrawn. If the revoker claims that the documents would

prove his case, then the Controller must look at the documents. This is, of course, subject to relevancy and admissibility.

MERITS:

13. Mr.Grover, learned Senior counsel for the appellant submitted that the statute does not provide for presumption of validity and therefore, once the opponent produces his prima facie evidence regarding novelty, inventive steps and other grounds, the initial burden is discharged by the opponent and onus shifts to the patentee. Learned counsel submitted that it is clear from the complete specification that interferons (IFNs) and particularly interferonα2a are pharmacologically active proteins with antiviral and antiproliferative activity. It is used in treating hepatitis and also other health problems. The other forms of pegylated interferonα are also known. It is also known that when proteins are conjugated to PEG, it improves the stability and solubility and reduces the immunogenicity. The clinical usefulness of PEG conjugated proteins is also known. The advantage of branched PEG conjugates over linear PEG conjugates is also known. The complete specifications clearly show that reagents of Formula 1 and Formula II may be obtained by conventional methods. Therefore, the increased antiproliferative activity and the decreased antiviral activity which are referred to as "surprising properties" are really not unexpected results.

14. Mr.Grover submitted that the European Patent No.0400472 ('472 - in short) marked as Ex. A and entitled 'Polyethylene Glycol Derivatives, Process for preparing the same and Modified Protein' taught that proteins

containing amino groups including various interferons could be conjugated with PEG to achieve the desired effects of pegylation. Ex.B "Distribution and Tissue Uptake of Poly (ethylene glycol) with Different Molecular Weights after Intravenous Administration to Mice" - (Yamaoka,et al) recommended a PEG-structure of a molecular weight of approximately 50,000 Daltons in order to achieve a sustained half-life and low organ accumulation. This prior art cannot be read narrowly as if it deals only with the impact of molecular weight on urinary clearance. Ex.C "Preparation of Long-Acting Superoxide Dismutase Using High Molecular Weight Polyethylene Glycol (41000-72000 daltons)" - (Somack,et al) discloses the value of obtaining high molecular weight PEG conjugates while maintaining a low degree of protein modification in order to retain the pharmacological effects of the protein. Before the Controller only an abstract of Ex.C was produced and the entire document was produced before us only at the time of appeal along with MP.No.111/2012. According to the learned senior counsel, Ex.C would indicate the applicability of the technique to other proteins including interferon. Ex.D, WO9511924 ('924 Patent) discloses a double or triple branched polymer conjugate. According to the learned counsel, '924 Patent taught a branched PEG structure linked to interferon. It discloses a methoxypolyethylene conjugate of lysine. It also taught various methods for the synthesis of branched PEG conjugates. The learned Senior counsel then referred to Ex.E "A Branched Monomethoxypoly (ethylene glycol) for Protein Modification" [Monfardini, et al] (Monfardini, in short). This is also referred to in the complete specification as a prior art. He submitted that this discloses the structure which is identical to the

structure in claim-1 of the invention. Learned counsel read out the extract of the disclosure contained in Monfardini to show that this methodology would be used for PEG chemistry in general. He submitted that therefore all these were known state of the art on the priority date of application and the claim Nos.1 to 10, 12 and 13 fail for lack of novelty.

15. Mr.Grover relied on Synthon BV v. Smithkline Beecham, plc., [(2005) UKHL59], where the Court held that where the very subject matter of the alleged invention has been disclosed, the question no longer is whether the prior disclosure contains all of the detailed instructions by which to arrive at the final result, but whether a person skilled in the art would, through trial and error, be able to achieve the final result. In Synthon case (cited supra), the Court held that the person skilled in the art is assumed to be willing to make trial and error experiments to get it to work. Learned senior counsel submitted that it is not open to the patentee to contend that Monfardini discussed only the pegylation of enzymes, and not the pegylation of interferon and a bare perusal of the structures of the claimed compounds and the Monfardini structure show that they are identical. According to the learned senior counsel, given the common general knowledge on the date of invention, Monfardini's disclosure of a polyethylene conjugate of PEG of lysine of molecular weight 40000 daltons linked to the required protein constitutes an enabling disclosure.

16. As regards inventive step, the learned senior counsel submitted that the Monfardini documents are really to be understood as statements of a person skilled in the art giving opinion on PEG chemistry. Learned

senior counsel then read out the complete specifications and submitted that it is evident from the complete specifications that the interferon 2a2 linear conjugates had increased activities when compared to native interferon a2a. This increase in the activity is only to be expected and obvious and there is nothing surprising about it. Learned Senior counsel in this regard referred to KSR v. Teleflex [550 US 398 (2006)]. Learned senior counsel submitted that the patentee has not shown how the alleged invention amounts to a technical advancement over and above what was already known in the state of the art. According to the learned senior counsel, when the Opposition Board has specifically held against the patentee, it was incumbent upon the Controller to give his findings on each of the exhibits and why those exhibits do not render the invention obvious. Learned senior counsel also submitted that when Monfardini said that the equivalent of R and R' is methyl, it would be obvious to one skilled in the art to substitute methyl with other alkyls such as, ethyl, propyl, butyl, etc. Learned counsel submitted that interferons are not excluded by Monfardini and relied on the judgment of the United States Court of Appeals for the Federal Circuit in Pfizer, Inc. v. Apotex, Inc. in 2006-1261 dated 22.3.2007. Learned senior counsel submitted that having held that the structure of the molecule of the claimed invention is deducible from the prior art and that when each part of the molecule is being known and the effects are known, the claim lacks novelty and inventive steps, taking into account the physiological activity of the bioactive compound which has changed appreciably when the bioactive compound is bound to a branched PEG, it was not open to the Controller to totally reverse the position only because the prior art suggests the use

of higher molecular weights for the purposes other than what is mentioned and claimed by the patentee. As regards the objection raised under S.3 (d) of the Act, learned counsel submitted that the burden is solely on the patent applicant and referred to the decision in Novartis AG v. Union of India [(2007) 4 MLJ 1153] where it was held that it is the duty of the patent applicant to show that the discovery had resulted in the enhancement of a known efficacy. Learned senior counsel submitted that the Hon'ble Madras High Court in the same judgment held that S.3 (d) requires showing of increased pharmacological effects. Therefore, according to the learned senior counsel for the appellant, the invention is merely a new form of pegylated interferon-a and it is for the patentee to demonstrate an enhancement in efficacy. Learned senior counsel submitted that it is not sufficient to compare the claimed invention with the non-conjugated interferon-a, but the inventor must compare the invention with other linear and branched conjugated interferon. He referred to the judgment of the IPAB in Novartis AG v. Union of India and others in TA1-5/2007/PT/CH dated 26.6.2009 where the Board held that to discharge the burden under S.3(d), the comparison ought to have been between the properties of imatinib mesylate and its beta crystalline form and not with imatinib base. Therefore, for the purpose of S.3 (d), the comparison ought to have been between the claimed invention and other linear/branched conjugates of interferon as they were admittedly known substances with known efficacy. This has admittedly not been done and the burden of proving the efficacy has not been discharged and therefore, the comparison is made in all the Examples 1 to 6, it would not advance the case of the patentee. Learned counsel submitted that the additional documents in Annexure A to C

without any accompanying affidavit by the experts will not by themselves prove the enhancement in efficacy. For all these reasons, the learned senior counsel submitted that the grant may be set aside.

17. Mr.D.J.Solomon, the representative of the first respondent submitted that it is for the appellant to prove each ground on which it claims that the invention is not patentable. He referred to Ss.101 and 102 of the Indian Evidence Act, 1872 regarding the burden of proof. He submitted that in a post-grant opposition, the threshold is higher since the patent is granted and if no fresh evidence is filed by the opponent and what is relied on are the materials which were before the Controller at the time of grant, the burden is much higher. He referred to the following decisions

(i) The General Tire & Rubber Company v. The Firestone Tyre and Rubber Company Limited & Ors. [1972 RPC 457], regarding the onus of proof.

(ii) The judgment of United States Court of Appeals for the Federal Circuit in 05-1313 dated 20.11.2006 [Impax Laboratories v. Aventis] regarding the quality of evidence.

(iii) Raj Parkash v. Mangat Ram Chowdhry and Ors. [AIR 1978 Del.1].

He submitted that the words used in Bishwanath Prasad Radhey Shyam v. Hindustan Metal Industries [PTC (Suppl) (1) 731(SC)], viz., 'validity of a patent is not guaranteed by the grant' should be understood in the context of that decision. He submitted that the Form of Patent (III Schedule) and the Form of Patent after the amendment of the Patent Rules in 2006, are different and the words 'validity of the patent is not guaranteed' has now been deleted in the amended Patent Rules. According to him, this could

only mean that the law-makers intended that there should be a presumption of validity. He submitted that in addition, in the present case, the Controller had considered the Opposition Board's recommendations and rejected them. Therefore, this grant shall not be set aside. He submitted that the closest prior art disclosed in Monfardini (referred to supra) is an admitted prior art and it was considered by the Examiner. The examination report which is in the Annexure-B would show how the respondent has met all the objections raised by the Controller. He then explained the following terms, proteins, enzymes, interferon, polyethylene glycols, pegylation, etc. Learned counsel submitted that the invention in question is for a physiologically active branched PEG-IFN α conjugate having the formula mentioned in the specification. He submitted that there are three elements to the claim-1, (a) it should be physiologically active; (b) it should be a branched PEG IFN α conjugate; and (c) average molecular weight of PEG is from 26000 to 66000 daltons. Mr.Solomon submitted that this invention has a much higher antiproliferative activity concomitant with decreased in vitro antiviral activity and increased circulating half-life plasma residence time and reduced immunogenicity and decreased clearance and all these have been explained in Examples 3 to 6 and Tables 1 to 4 of the complete specification. To support his case regarding novelty, he relied on

(i) The General Tire & Rubber Company v. The Firestone Tyre and Rubber Company Limited & Ors. [1972 RPC 457],

(ii) Judgment of United States Court of Appeals for the Federal Circuit in 05-1313 dated 20.11.2006 [Impax Laboratories v. Aventis] and

(iii) Apotex Inc. v. Sanofi (2006 FCA 421)

He submitted that the structure of the claim-1 may be similar to the Morfandini structure but certainly not identical. To anticipate the claimed invention, each and every element of the claim should be explicitly disclosed in a single prior air document. He submitted that the term, 'protein' covers a myriad of compounds which vary both in their function, size, structure, etc. Therefore, the fact that Monfardini shows a similar structure does not mean that it anticipates the invention. Learned counsel also referred to certain observations in Synthon BV v. Smithkline Beecham Plc [(2005) UKHL 59] and submitted that there was no explicit and clear disclosure as laid down in Synthon case. He submitted that the Controller had correctly held that since such a molecule has not been directly disclosed in the prior art, the structure passes the novelty.

18. As regards inventive step, he relied on the decisions in

(a) The General Tire & Rubber Company v. The Firestone Tyre and Rubber Company Limited & Ors. [1972 RPC 457], "It seems to me to be very dangerous and in law not permissible to assess obviousness in the light of carefully selected pieces of prior knowledge"

(b) Technograph Printed Circuits Limited v. Mills &Rockley (Electronics) Limited [1972 RPC 346], "But the question is whether it would have been obvious to the unimaginative skilled technician>."

(c) Dyson Appliances Ltd. V. Hoover Ltd. (2002 RPC 465), here the Court explained the Windsurfing principles and that: the Court must remove from its mind that patented solution. Hind-sight reasoning must be avoided."

(d) Star scientific, Inc. v. R.J.Reynolds Tobacco Company & Anr. [United States Court of Appeals for the Federal Circuit in 2010-1183, dt.26.8.2011],"Obviousness cannot be based on the hindsight combination of components selectively culled out from the prior art to fit the parameter of the patented invention."

(e) Unigene Laboratories, Inc. & Anr. V. Apotex Inc. & Anr. [United States Court of Appeals for the Federal Circuit in 2010-1006, dt.25.8.2011], It must be shown that" a person of ordinary skill at the time of the invention would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention."

(f) The Procter & Gamble Company v. Teva Pharmaceuticals USA, Inc. [United States Court of Appeals for the Federal Circuit in 2008-1404, 1405, 1406, dt. 13.5.2009] The Court held that clear and convincing evidence must be furnished.

(g) T-0970/00 – Board of Appeal of the EPO dated 15.9.2004 [In the case of Murata Manufacturing Co.Ltd.] t held that prior disclosure must not be distorted or misinterpreted based on hindsight knowledge that it artificially meets the specific claims recited in the invention."

(h) T-0311/93 – Board of Appeal of the EPO dated 16.1.1997 [In the case of Kanegafuchi Kagaku Kogyo Kabushiki Kaisha v. Suntory Limited/ Shiratori Pharmaceutical Co. Ltd.] and

(i) Apotex Inc. v. Sanofi-Synthelabo Canada Inc & anr. [2006 FCA 421] In this case the Court held that the facts showed the impossibility of predicting the calimed advantages and the difficulty in producing the claimed compounds.

He submitted that to prove obviousness, the appellant ought to have filed the evidence of an Expert to show why the invention is not taught by the prior art documents and that it was based on common general knowledge. The appellant cannot defeat the invention by cleverly picking and choosing the selected portions or features from each of the prior art documents. He submitted that '472 Patent was to provide PEG derivative with high purity, using cyanuric chloride as the linker. A laundry list of proteins was disclosed and the examples show PEG of 5000 MW and no data relating to activity of IFN or pegylated IFN is reported in the example (Ex.20). Therefore, this prior art does not render the invention obvious. As regards Ex.B, he submitted that this prior art is to study the molecular weight of PEG on the half-life in the circulation and on the organ distribution of PEG.

According to Mr.Solomon, no experimental data is provided relating to biological activities of any therapeutic molecule modified with PEG of any MW. He submitted that in fact, this prior art concludes that the expression, 'provided each drug molecule carries only one PEG chain' teaches away from the invention. He submitted that Ex.C teaches linear or multi-linear pegylation for SOD, but this has nothing to do with this invention. As regards Ex.D-'924 Patent, this actually records that excessive polymer conjugation results in loss of activity and therapeutic usefulness of the biologically active material. According to this, the branched polymers are more suitable for therapeutic agents having few available attachment sites for polymer conjugation. As regards Monfardini, he submitted that though enzymes or IFN are proteins, their activities and mode of action are different. Even though branched pegylation was known in 1990, the researchers suggested that the linear pegylation and multi-linear pegylation are recommended. In all the examples, 5000 MW per chain was used. Therefore, there was no clear direction as to the type of pegylation and the effect of pegylation and in fact, it suggested and recommended single point attachment. Therefore, the persons skilled in the art would not have applied the teachings of Monfardini since there is absolutely no expectation of success. He also submitted that a person skilled in the art would have never come to the conclusion that the branched pegylation is always better than unmodified or linear for all enzymes. According to him, a person skilled in the art would not be motivated to adapt the teachings of Monfardini. According to Mr.Solomon, at the best, the persons skilled in the art may have thought that the branched pegylation may be considered in PEG chemistry due to single

point of attachment. Further, Monfardini also confirms that branched pegylation with single site of attachment is most suitable for modifying biological materials having only one or very few attachment sites, but IFN has 11 lysine sites for attachment. He also submitted that Monfardini disclosed that the behaviour of enzymes is under active consideration and therefore, the teaching of Monfardini cannot be generalized even to all enzymes. He submitted that the Controller had clearly construed that Monfardini will not destroy the patentability of invention and Monfardini cannot be interpreted out of context. He submitted that in determining obviousness ex-post facto analysis should not be entertained and hindsight acceptance of obviousness is not permitted. The two main points on which the respondent urged that the grant must not be set aside were, (a) none of the prior arts encourage the use of a MW of 40,000 daltons; and (b) every protein exhibited different responses and activities to PEGylation so the prior arts relating to enzymes and superoxide dismutase cannot destroy the novelty and non-obviousness.

19. As regards section 3(d) of the Act, it was submitted that the appellant has taken two different stands to apply this provision. He has treated the invention as a new form of known interferon-α and also as a new form of Monfardini PEG conjugates. According Mr.Solomon, the branched PEG interferon-α conjugate is directly derived from the unmodified interferon-α and not from linear PEG interferon-α conjugate. It is technically impossible to arrive at branched PEG IFN-α conjugate starting from linear PEG IFNα conjugate. Therefore, the known substance for the present case is unmodified interferonα and it is enough

if the respondent shows that the branched PEG interferonα conjugate has enhanced efficacy compared to the known efficacy of unmodified interferonα. According to him, Example-3 and Table-2 clearly show that in vitro antiproliferative activity of the branched interferonα conjugate is 28 fold higher than the unmodified IFNα. Example-6 of the specification shows in vivo antiproliferative activity of the branched PEG interferonα conjugate over the modified interferonα. According to him, there is a significant reduction in ACHN tumor size and G402 tumor size for weekly dose levels of 60, 120 and 300 µg compared to the same dosage administered three times per week of unmodified IFNα. He submitted that in vitro and in vivo antiproliferative activities are therapeutic activity which indicates the healing of tumor and this shows enhanced efficacy as held by the Hon'ble Madras High Court in Novartis AG case (cited supra). He submitted that the conjugate means a product which is obtained by pegylating a polymer such as PEG derivative with a biological molecule such as protein. Monfardini disclosed the branched PEG conjugate of four enzymes and therefore, the appellant's argument that the present invention is a new form of Monfardini PEG conjugate is incorrect. He submitted that the words, 'invention is a new class of PEG derivatives of interferonα' cannot be construed to mean that it is a derivative of known PEG interferonα conjugate. He submitted that the appellant had not pleaded in the written statement filed before the Controller that the branched PEG IFNα conjugate is a new form of linear PEG IFNα conjugate. Therefore, for the purpose of S.3 (d), branched PEG IFNα conjugate cannot be dealt with as a new form of linear conjugate of IFN α. He submitted that the facts in Novartis case (IPAB) cited supra, were

totally different. In that case, the known substance for beta crystal form of imatinib mesylate will be imatinib mesylate and not imatinib base. But, in this case, the comparison should be between branched pegylated interferon conjugate and linear pegylated interferonα. He referred to Harris article and Bailon article marked as Ex.B and Ex.C filed with the reply statement to show the comparative efficacy of unmodified interferon linear PEG (5 KD) and linear PEG(12 KD) and branched PEG (40 KD). He submitted that the present application was filed in the year 1997 whereas section 3(d) was introduced in the 2005. Learned counsel submitted that the invention does not fall under S.3(e). According to him, branched PEG conjugate is conjugated to a particular attachment site of IFNα through a chemical reaction that takes place between these two components and it cannot be termed as a mere admixture. As regards insufficiency, he relied on Dual Manufacturing and Engineering Inc.'s Patent [1977 RPC 189]. In conclusion, it was submitted that there was no justification to interfere with the order of the Controller.

20. In this case, as we have earlier observed, there were two decisions. The Opposition Board made two recommendations. The conclusion under each head though different in the recommendations of the Opposition Board, it was held that the patent should not be revoked. The Controller was not persuaded by the recommendations and proceeded further and rejected both the objections. The evidence marked in M/s.WOCKHARDT LTD. opposition was submitted before us as Exhibits along with the counter statement. The crucial evidence in this case was in the form of affidavits of two experts But, neither in the oral

submissions or in the written submissions did the counsel referred to those affidavits. Their arguments centered mainly on Monfardini and the appellant referred to the complete specification itself to show what the common general knowledge was at the time of invention. Other Exhibits viz., Patent-472 and Somack et al were all referred to. We will be referring to them later.

21. Now we will extract the complete specification as under:

TITLE

"A Physiologically Active Branched Peg-IFNα Conjugate"

Interferon, in particular interferonα2a, is a pharmaceutically active protein which has antiviral and antiproliferative activity. For example interferon is used to treat hairy cell leukemia and Kaposi's sarcoma and is active against hepatitis. In order to improve stability and solubility and reduce immunogenicity, pharmaceutically active proteins such as interferon may be conjugated to the polymer polyethylene glycol (PEG).

The bioavailability of protein therapeutics are often limited due to their short plasma half-life, this preventing them from attaining their maximum clinical potency. In recent years, PEG conjugated biomolecules have been shown to possess clinically useful properties [Inada et al., J. Bioact. And Compatible Polymers 5, 343 (1990); Delgato et al., Critical Reviews in Therapeutic Drug carrier Systems 9, 249 (1992); Katre, Advanced Drug Delivery Systems 10, 91 (1993)]. Among these are better physical and thermal stability, protection against susceptibility to enzymatic degradation, increased solubility, longer in vivo circulating half-life, decreased clearance and enhancing potency. It has been reported that branched PEG conjugates exhibit increased pH and thermal stability and greater stability towards proteolytic digestion than linear PEG conjugates. [Monfardini et a., Bioconjugate Chem. 6, 62

(1995)]. Other properties of PEG proteins are reduced immunogenicity and antigenicity, as well as reduced toxicity. Another effect of PEGylation of certain proteins may be reduced in vitro activity accompanied by enhanced in vivo activity. This has been observed in G-CSF [Satake-Ishikawa et al., Cell Structure and Function 17, 157-160 (1992)], IL-2 [Katre et al., Proc. Natl. Acad. Sci. USA 84, 1487 (1987)], TNF-α [Tsutsumi et al., Jpn. J. Cancer Res. 85, 9 (1994)], IL-6 [Inoue et al., J. Lab. Clin.Med.124, 529 (1994)] and CD4-IgG [Chamow et al., Bioconj. Chem. 5, 133 (1994)], among others.

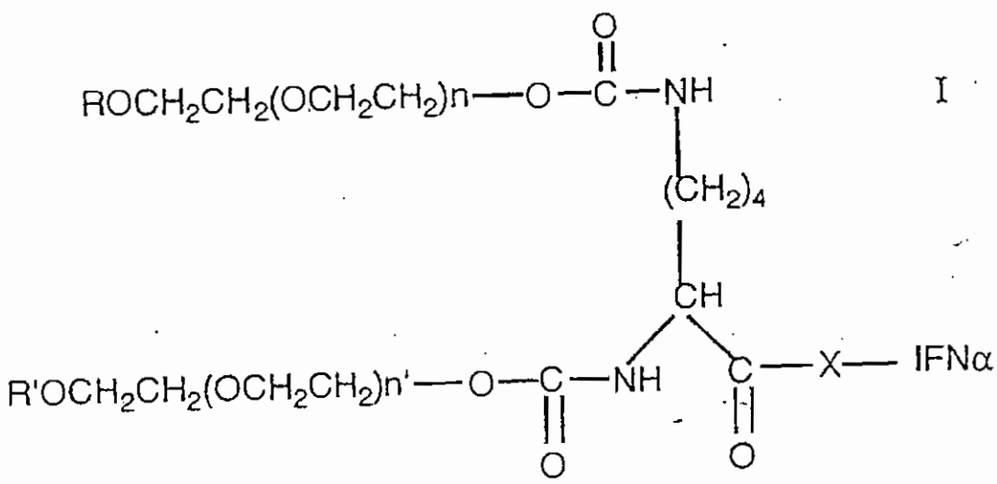
It has been now observed that in the case of interferon, PEGylation reduces in vitro antiviral activity but increases antiproliferative activity in human tumor cells. However the new PEG interferon conjugate of this invention has surprising properties in that the antiproliferative activity of the PEG interferon is much higher than that not only of interferon but of other PEG interferon conjugates. Although the antiproliferative activity of the conjugate is much increased over other PEG interferon-α conjugate of this invention is non-immunogenic, it elicits virtually no antibody formation. In contrast, other PEG interferon-α conjugates do elicit limited antibody formation.

Accordingly, the invention is a new class of PEG derivatives of interferonα (IFNα). The conjugate of this invention has a branched PEG structure, as can be seen below. The branched PEG has the advantage of allowing the attachment of 2 linear PEG molecules at a single site, thus doubling the attached PEG mass without multiple sites of PEGylation.

Compared to unmodified IFNα [i.e., IFNα without a PEG attached], the conjugate has an increased circulating half-life and plasma residence time, reduced immunogenicity, decreased clearance and increased antiproliferative activity, concomitant with increased in vitro antiviral activity. Compared with other PEG-IFNα conjugates the conjugate of this invention has a much greater antiproliferative activity, disproportionate to the enhancement

reduction that occurs in its other characteristics, and virtually no immunogenicity.

The physiologically active PEG-IFNα conjugate species of this invention has the formula:



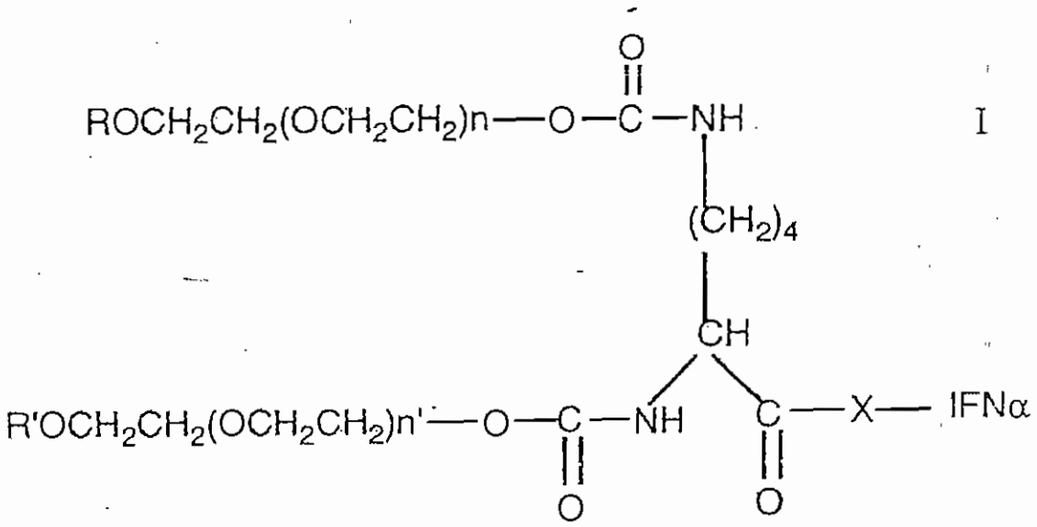
I

The conjugate of this invention has the same uses as IFNα, for example, antiproliferative uses. In particular, the PEG interferon-α conjugates of this invention are useful to treat immunomodulatory disorders such as neoplastic diseases, for example, hairy cell leukemia, CML, and Kaposi's sarcoma, and infectious diseases, in the same way IFNαs (especially IFNα2a) are used to treat these diseases. However, the conjugate of this invention has improved properties including superior stability, greater solubility, enhanced circulating half-life and plasma residence times. In addition, these conjugates have antiproliferative activity which is superior to IFNα. Also as noted the conjugate shows a surprising dissocioation of antiviral and antiproliferative effects. This property is additionally useful to enhance a desired activity of a conjugate, while decreasing or eliminating an undesired activity. For example, if an undesired side effect is associated with the antiviral activity, eliminating this activity

would eliminate the side effect, while retaining the antiproliferative activity. Therefore, the present invention also comprises the pharmaceutical compositions on the basis of the compounds of formula I or their salts and to methods for producing them.

The pharmaceutical compositions of the present invention used in the control or prevention of illnesses comprises an interferon conjugate of the general formula I and a therapeutically inert, non toxic and therapeutically acceptable carrier material. The pharmaceutical compositions to be used can be formulated and dosed in a fashion consistent with good medical practice taking into consideration the disorder to be treated, the condition of the individual patient, the site of delivery of the protein conjugate, the method of administration and other factors known to practitioners.

The claimed conjugate is a physiologically active PEG-IFNα conjugate having the formula



I

Where R and R^1 are independently lower alkyl; X is NH or O {X is at least one of the functional groups in the IFNα molecule selected from NH_2 or OH); n and n^1 are integers having a sum of from 600 to 1500; and the average molecular weight of the polyethylene glycol units in said conjugate is from about 26000 daltons to about 66000 daltons. The conjugate of formula I has a branched structure, in that two PEG moieties are attached ot the protein via a single linkage.

The numbers n and n^1 are selected such that the resulting conjugate of Formula I has a physiological activity of IFNα, which activity may represent the same as, more than, or a fraction of the corresponding activity of unmodified IFNα. n and n^1 (n and n^1 may be the same or different) represent the number of ethylene glycol units in the PEG. A single PEG unit of OCH_2CH_2 has a molecular weight of about 44 daltons. The molecular weight of the conjugate (excluding the molecular weight of the IFNα) depends on the numbers n and n^1. The sum of n and n^1 for the conjugate of Formula I is from 600 to 1500, producing a conjugate having a total average molecular weight of PEG units of from about 26000 to 66000 and preferably from about 35000 to 45000 daltons and especially about 39000 to 45000 daltons, with 40000 daltons especially preferred. A preferred sum of n and n^1 is from about 800 to 1200, with the average sum being from about 850 to 1000, and a preferred sum being about 910. Either of n and n^1 may individually be 420 or 520, or both may be 420 or 520 or both may be 455. The preferred ratio of n to n^1 is from about 0.5 to 1.5, with an especially preferred ratio of from about 0.8 to 1.2. A molecular weight of "about" a certain number means that it is within a reasonable range of that number as determined by conventional analytical techniques.

Also preferred is a conjugate of Formula I where IFNα is IFNα2a, a conjugate where R and R^1 are methyl, a conjugate where X is NH, and a conjugate where n and n^1 are individually or both either 420 or 520. Such a conjugate having all the above characteristics is especially preferred.

R and R^1 may be any lower alkyl, by which is meant an alkyl group having from one to six carbon atoms such as methyl, ethyl, isopropyl, etc. Branched alkyls are included. A preferred alkyl is methyl. With regard to the two PEG groups of Formula I, R and R^1 may be the same or different.

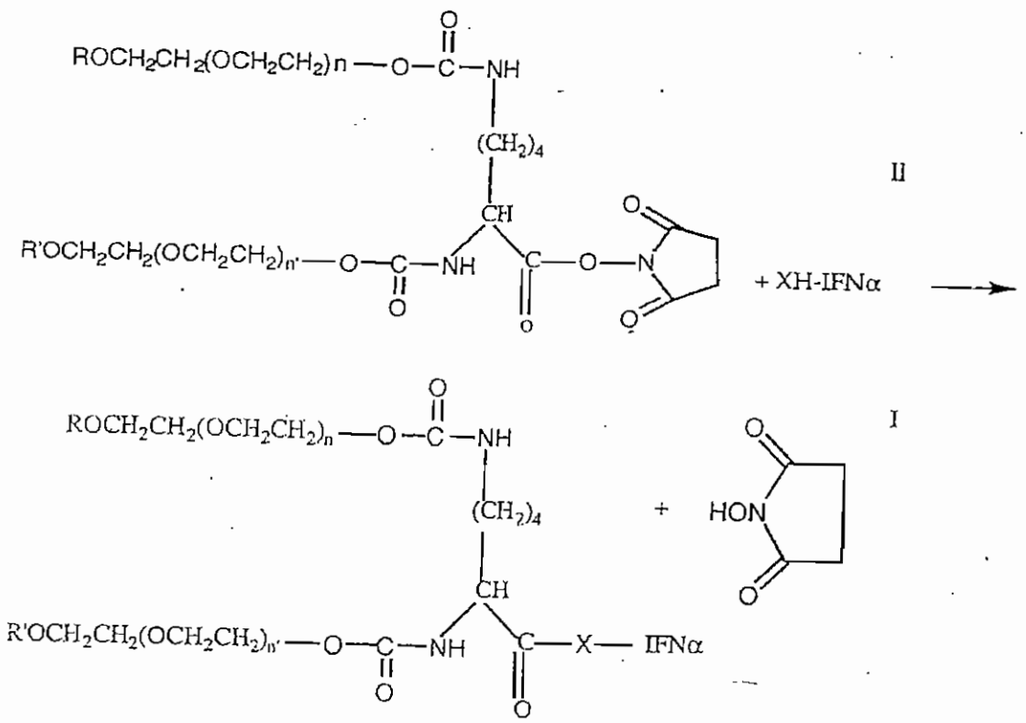
By IFNα (interferon α) and its species IFNα2a is meant the natural or recombinant protein, preferably human, as obtained from any conventional source such as tissues, protein synthesis, cell

culture with natural or recombinant cells. Any protein having the activity of IFNα, such as muteins or otherwise modified proteins, is encompassed. Obtaining and isolating IFNα from natural or recombinant sources is well known [Pestka, Arch. Biochem. Biophys. 221, 1 (1983)]. A preferred IFNα is IFNα2a, which as stated above, is obtained by known methods [Pestka, Sci. Am. 249, 36 (1983); European Patent No.43 980)].

The physiologically active conjugate of Formula I has IFNα activity, by which is meant any fraction or multiple of any known IFNα avtivity, as determined by various assays known in the art. In particular, the conjugates of this invention have IFNα activity as shown by antiproliferative activity against tumor cells and antiviral activity against cells infected with a virus. These are known activites of IFNα. Such activity in a conjugate can be determined by assays well known in the art, for example the assays described below [see also Rubinstein et al., J. Viron. 37, 755 (1981); Borden et al., Canc. Res. 42, 4948 (1982)]. Part of this invention is a conjugate of Formula I which has greater antiproliferative activity and less antiviral activity than unmodified IFNα.

The conjugate of Formula I is produced by covalent linkage of IFNα to PEG which has been activated by replacement of the PEG hydroxyl with a linking group, forming a reagent which is an N-hydroxy succinimide ester derivative of PEG (in particular monomethoxy PEG) of Formula II. The reagent may be obtained by conventional methods (Monfardini et a., supra). Linkage is via an amide or ester bond. In a preferred conjugate, linkage is via an amide bond (X is NH). Part of this invention is a method for increasing the antiproliferative activity of IFNα while reducing the antiviral activity of the IFNα, by linking the IFNα as described above to a reagent of Formula II to produce a PEG-IFN conjugate.

X represents the attachment site on IFNα by which the PEG reagent of formula II is covalently attached to the IFNα. The reagents attach to primary amino groups ($XH=NH_2$) on for example lysine or to the N-terminus of the IFNα. The reagents can also attach to a hydroxyl (XH=OH) on for example serine.



The reagent of formula II (PEG2-NHS), in which a total of 2 mono-methoxy PEG (m-PEG) chains are linked to lysine, one each at the α and € amino groups via carbamate (urethane) bonds and having the lysine carboxyl group activated to a succinimidyl ester, may be obtained by conventional methods, according to known procedures (Monfardini et al., supra) applicable to a reagent with R and lower alkyl, and a desired n. The reagent may be obtained from Shearwater Polymers, Inc. (Huntsville, Alabama). The preferred average MW of the PEG obtained is about 20000 daltons, providing a total PEG mass of about 40000 daltons in PEG2-NHS (other MWs may be obtained by varying n for the PEG-alcohol starting materials for the reagent of Formula II, by conventional methods).

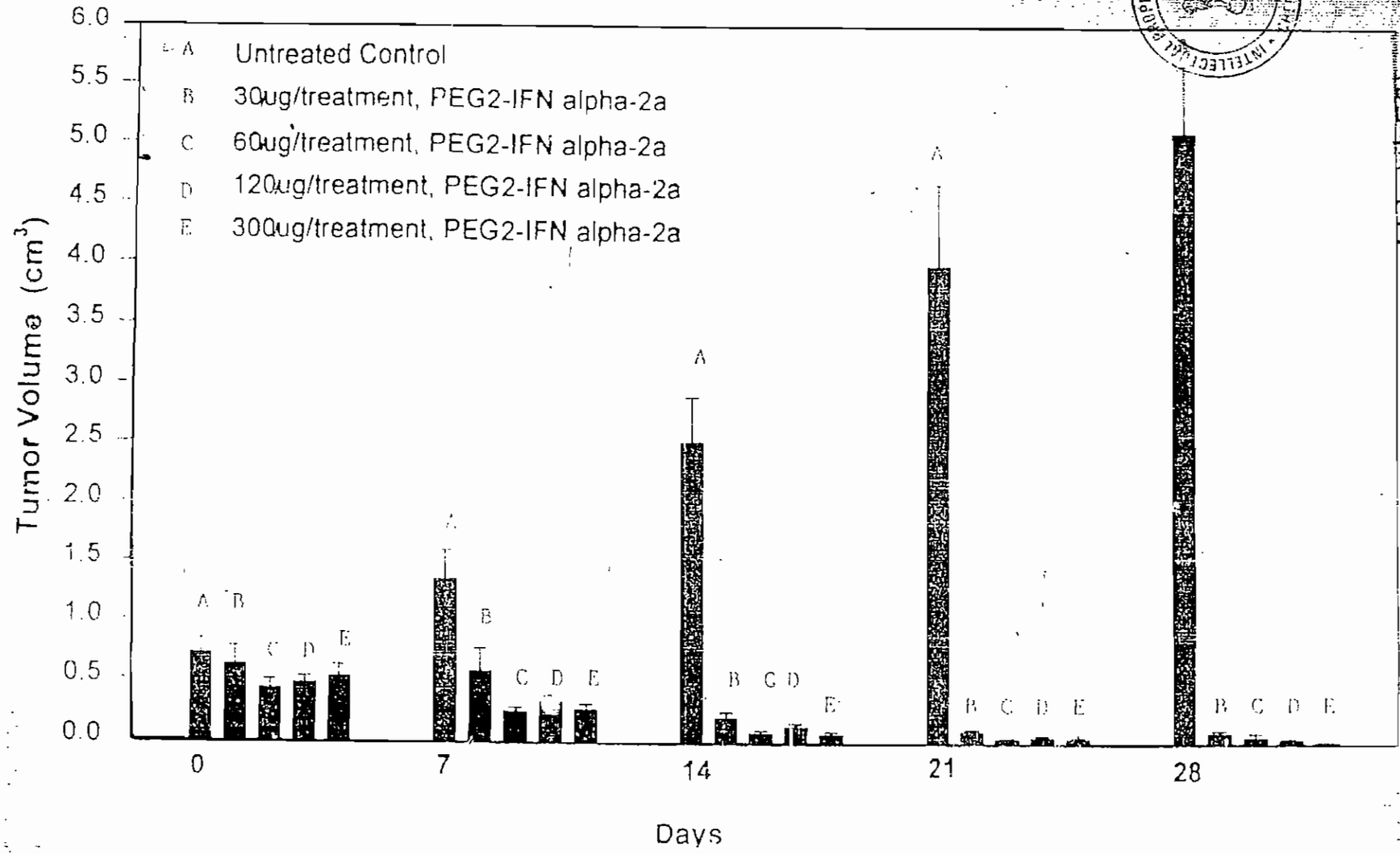
The reagent of formula II may be conjugated to IFNα by conventional methods. Specifically, the reagent of Formula II primarily reacts with one or more of the primary amino groups (for example N-terminus and lysine side chains) of IFNα (for example IFNα2a) to form an amide linkage between the IFNα and the

polymer backbone of PEG. The PEGylation reaction can also take place between PEG2-NHS and the free (if any) hydroxyl groups (for example serine) of IFNα to form an ester linkage. The reaction mechanism is shown above. The reaction conditions are conventional to a skilled person and are provided in detail below. The PEG reagent is combined with IFNα under mildly basic conditions at low temperature under conditions suitable for a nucleophilic substitution which will produce the conjugate of Formula I. This is also shown in the above reaction mechanism.

Attaching the reagents to IFNα may be accomplished by conventional methods. PEGs of any selected MW of this invention may be used. Reaction conditions may be selected to provide the claimed conjugate with one reagent attached. The conjugate of Formula I, which has a single reagent of Formula II attached, is separated from unmodified IFNα and conjugates having attached more than one reagent molecule by conventional methods. Purification methods such as cation exchange chromatography may be used to separate conjugates by charge difference, which effectively separates conjugates into their various molecular weights. The content of the fractions obtained by cation exchange chromatography may be identified by molecular weight using conventional methods, for example, mass spectroscopy, SDS-PAGE, or other known methods for separating molecular entities by molecular weight. A fraction ghen is accordingly identified which contains the conjugate of Formula I purified free from unmodified IFNα and from conjugates having more than one reagent attached. In addition, thereagents of Formula II release one lysine per reagent upon acid hydrolysis, so that the number of lysines in the hydrolysis indicates the number of PEGs attached to the protein, thus the number of reagent molecules attached to a conjugate may be verified.

The description of the drawings are as follows:

FIGURE 1



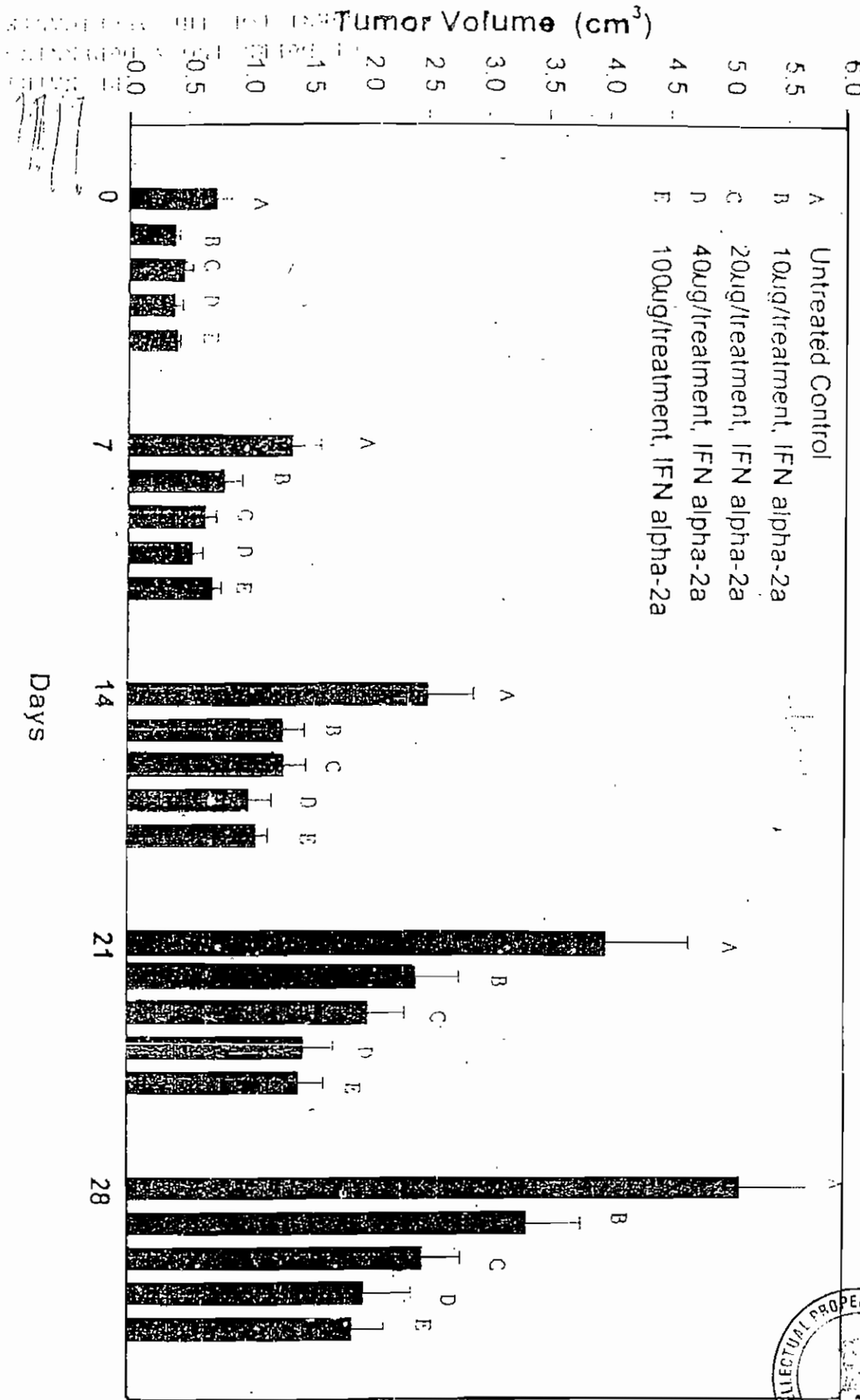


FIGURE 2

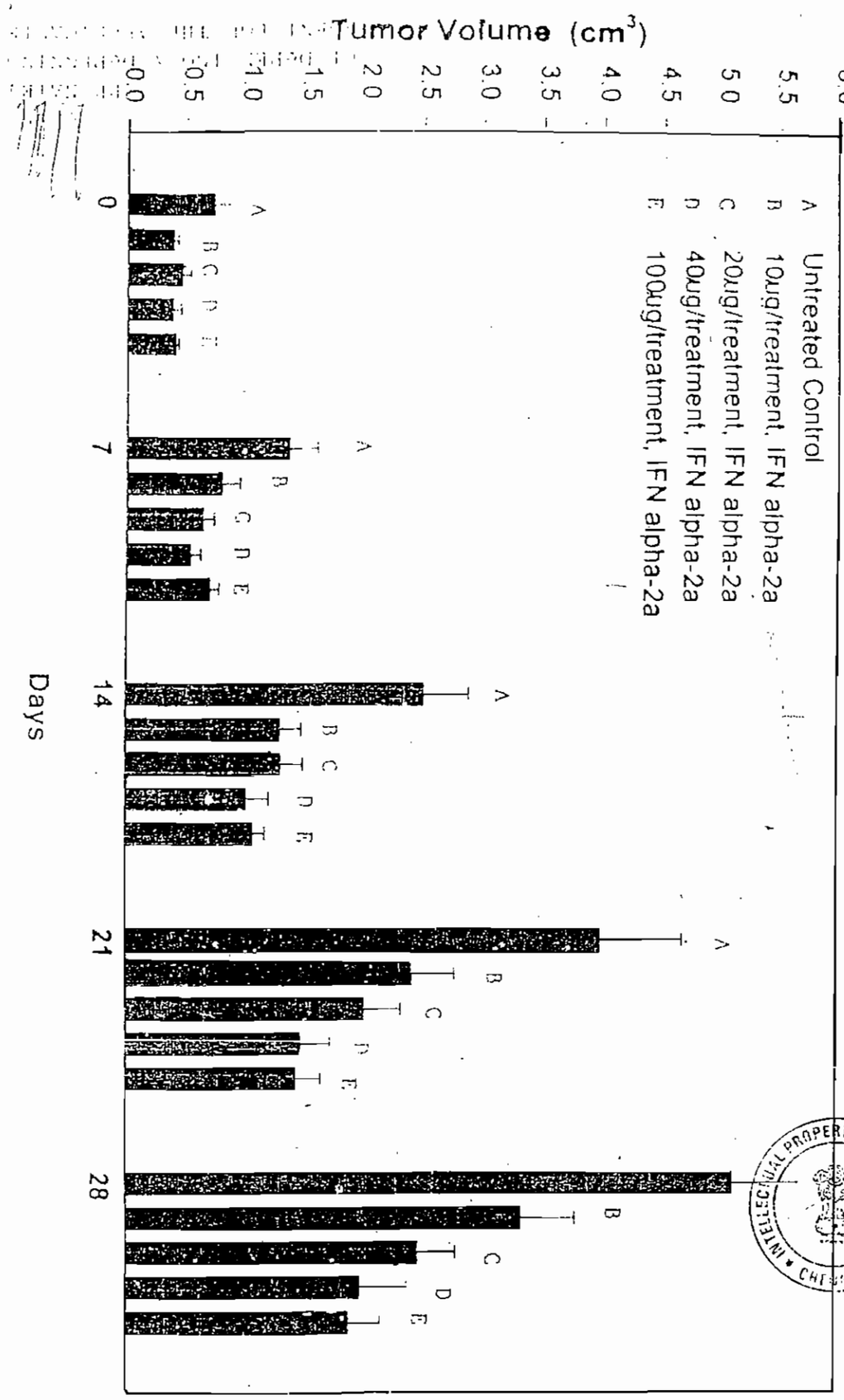


FIGURE 2

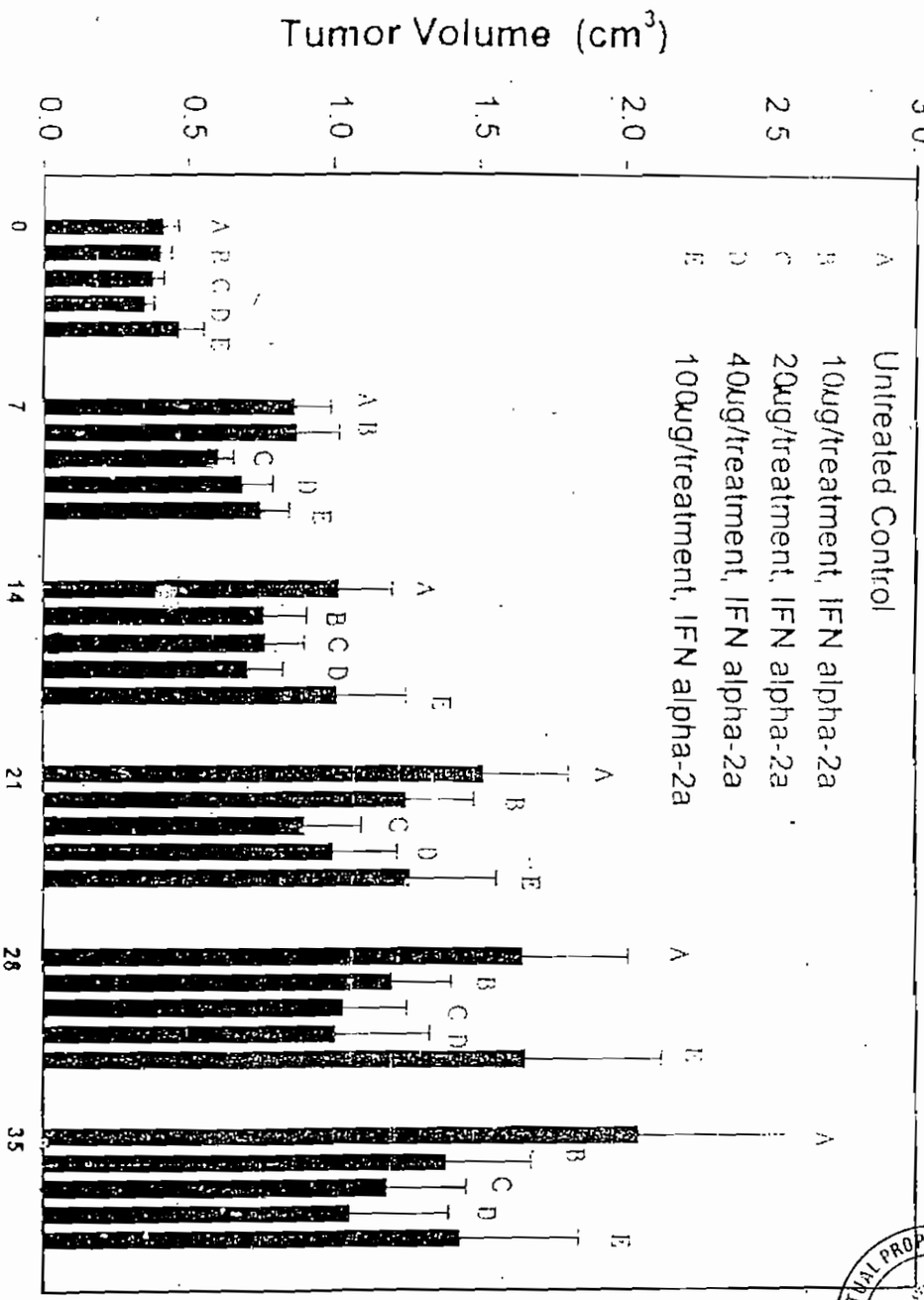


FIGURE 4

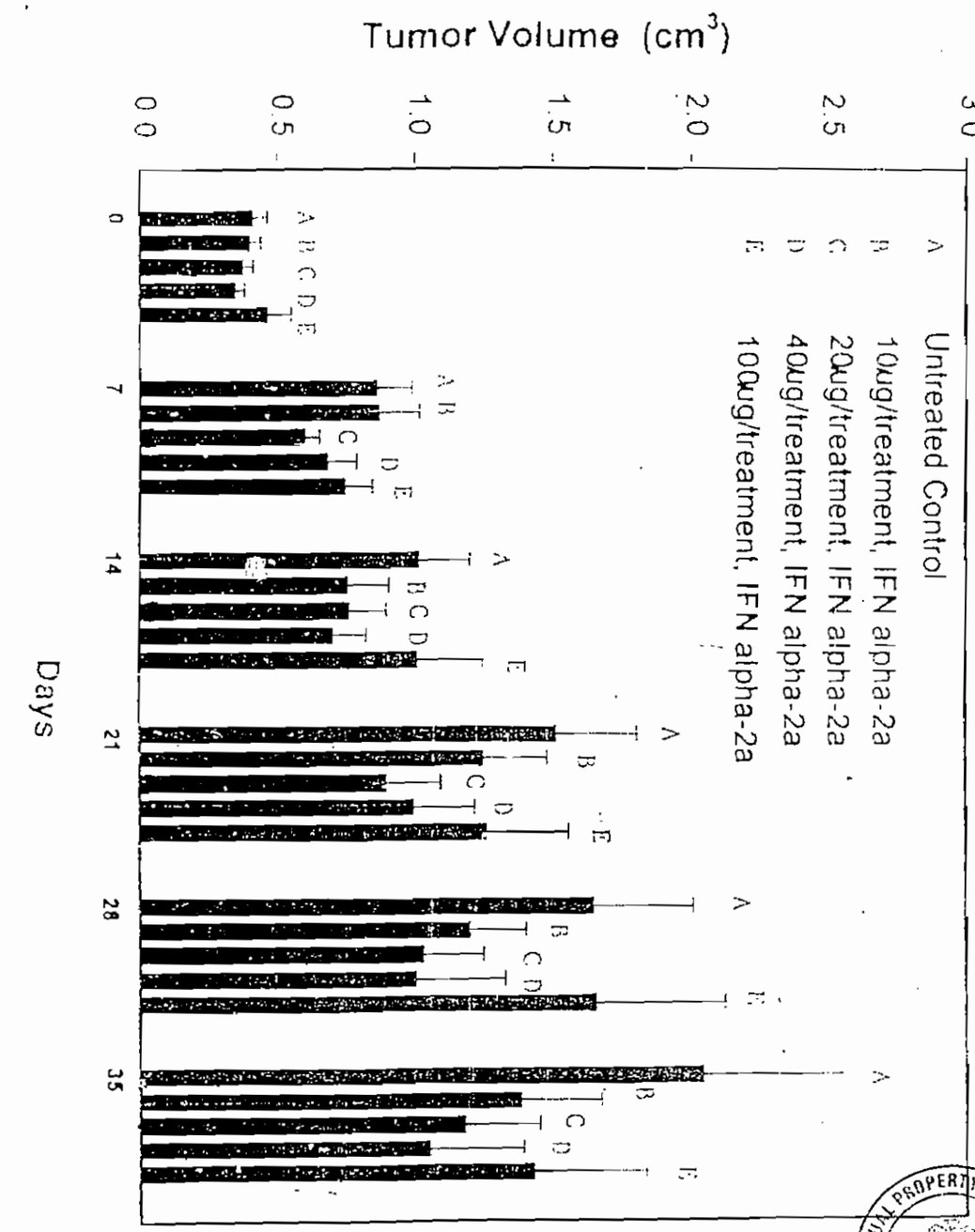


FIGURE 4

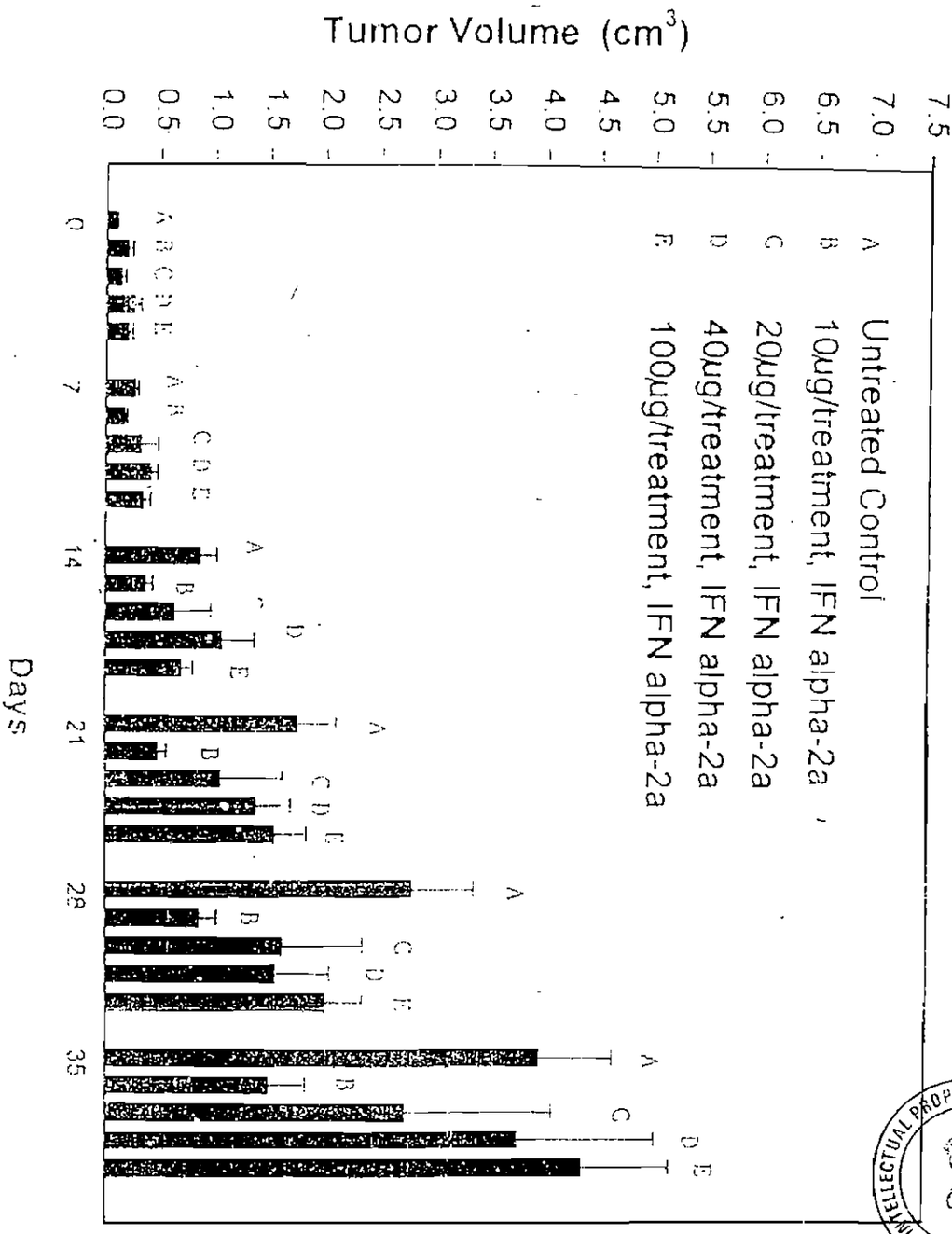


FIGURE 6

1632/Mar/97

Example-3

In vitro Bioactivities of conjugate of Formula I

xxxx
xxxx
xxxx

Table 2

In vitro antiproliferative activities in human Daudi (Burkitt's lymphoma) cell lines.

Sample	Antiproliferative IC50 (ng/ml)	Activity Increase
IFNα2a	0.56	1x
Conjugate of Formula I	0.02	28x

Example-5

Immunogenicity

Normal BDF-1 mice (ten per group) were injected intraperitonially once per day five times per week with various interferon preparations having 300,000 units of antiviral activity. Some mice were also injected with aggregated form of IFNα2a which is more immunogenic than the monomer form. Blood samples were taken 19 days following the last injection and the serum was evaluated for neutralizing antibodies.

As seen in Table 4, mice injected with IFNα2a produced neutralizing antibodies and this response was greatly increased in mice injected with interferon aggregates. No antibodies were detectable in the majority of animals injected with the conjugate of this invention.

Table 4

Immunogenicity

Treatment	Antibody (INU/ml)*	
	Median	Range
IFNα2a	2,400	217-8,533
IFNα2a Aggregates	42,667	8,000-768,000

* Interferon neutralizing units/ml.

22. We Claim

1. A physiologically active branched PEG IFNα conjugate having the formula (the same formula extracted earlier in page), wherein R and R' are independently lower alkyl; X is NH or O; n and n' are integers having a sum of from 600 to 1500; and the average molecular weight of the polyethylene glycol units in said conjugate is from 26,000daltons to about 66,000 daltons.

2. A conjugate of claim 1 wherein the molecular weight of the polyethylene glycol units is from about 35,000 units to about 45,000 units.

3. A conjugate of claim 2 wherein the molecular weight of the polyethylene units is about 40,000 daltons.

4. A conjugate of claim 1 wherein R and R' are methyl.

5. A conjugate of claim 1 wherein X is NH.

6. A conjugate of claim 1 wherein the IFNα is IFNα2a.

7. A conjugate of claim 1 wherein the average sum of n and n' is 850 to 1000.

8. A conjugate of claim 1 wherein R and R' are methyl, X is NH, IFN α is IFN α2a and one or both of n and n' is 420.

9. A conjugate of claim 1 wherein R and R' are methyl ; IFN α is IFN α 2a; and one or both of n and n' is 520.

10. A conjugate of claim 1 which had greater antiproliferative activity than IFNα and less antiviral activity than IFNα.

11. A method for producing a PEG-IFN α conjugate having an increased anti-proliferative activity and decreased antiviral activity as compared to

IFNα, which method consists of covalently linking a reagent of Formula II to IFNα to produce said PEG –IFN α conjugate.

12. Pharmaceutical compositions comprising a PEG-IFNα as claimed in anyone of claims 1-10 and a therapeutically inert carrier.

13. A physiologically active branched PEG-IFN conjugate substantially as herein described with reference to the accompanying drawings.

These are the claims.

23. Annexure-C filed by the respondent along with its written submissions which is more like a glossary states that interferon is a class of proteins produced by the body as part of its natural defensive response on exposure to a foreign constituent like, viruses, microbes and tumor cells. They are molecules which signal the body's immune system and trigger the defensive mechanism to kill pathogens or tumors. The unmodified IFNα has several disadvantages such as, rapid absorption which leads to sharp increase in serum concentration which might result in fatigue, headache, muscle pain, fever, etc. It removes rapidly from the body because, it quickly clears from the kidney. There is large volume of distribution. It is broken down by proteolytic enzymes and its serum half-life is in 4 to 6 hours. Half-life of a drug is the time that it takes for the plasma concentration of drug to be reduced by half. The volume of distribution is the relationship between the amount of drug in the body and the amount of drug in the blood or plasma. The disadvantages abovementioned necessitated the frequent administration of interferonα to maintain the effective concentration. Due to short plasma half-life, the bioavailability of protein therapeutics is limited. Therefore, they do not

attain their maximum clinical potency. Therefore, these disadvantages had to be addressed. It is also known from the date of invention which is 31.5.1996 that interferon is conjugated to the polymer polyethylene glycol (PEG) in order to improve stability and solubility and reduce immunogenicity. PEGs are inert, water soluble, non-toxic polymers produced by linking repeated ethylene oxide subunits. PEGs have a wide range of application in many industries and in pharmaceutical industry, they are used in medicines to enhance the delivery of therapeutic peptides and proteins through a process known as pegylation. Pegylation is the process of attachment of one or more PEGs to another molecule. There could be a linear PEG which is a single chain of the individual units, or a long chain linear PEG which is a longer chain compared to the former, or multiple linear PEGs which has many chains attached in many attachment sites or branched PEGs which has two or more chains attached at a single site and hence called a branch.

24. From the complete specifications we find that the following factors may be taken to be within the common general knowledge. The interferon is a pharmaceutically active protein which has antiviral and antiproliferative activity. It was also known that interferonα2a which we are concerned with was in particular a similarly active protein with the same activity. Interferon was known to be useful to treat hairy cell leukemia and Kaposi's sarcoma. It was active against hepatitis-C.

25. Even in 1990, it was known that PEG conjugated biomolecules have certain clinically useful properties. These are, (i) better physical and

thermal stability, (ii) protection against susceptibility to enzymatic degradation, (iii) increased solubility, (iv) longer in vivo circulating half-life, (v) decreased clearance and (vi) enhancing potency. It was also known at the time of invention that branched PEG conjugates had increased pH and thermal stability and greater stability towards proteolytic digestion than linear PEG conjugates. PEG proteins were also known to have reduced immunogenicity and antigenicity and reduced toxicity. It was also known on the date of invention that pegylation of some proteins may result in reduction of in vitro activity along with the enhanced in vivo activity. It was also known that the pegylation of interferon reduces in vitro antiviral activity but increases antiproliferative activity in human tumor cells. These are all admittedly common general knowledge on the date of invention **and therefore improved activity could not have been a surprise it was expected.**

26. But, the specification declared that **this new PEG interferon conjugate** of this invention has surprising properties, i.e., its antiproliferative activity is much higher than that not only of interferon but of **other PEG interferon conjugates** as well. Though the antiproliferative activity is more increased, the reduction in antiviral activity is the same. Further, according to the inventor, this invention has **virtually no antibody formation**, while other PEG interferon alpha conjugates elicited **limited antibody formation**.

27. According to the invention, this is a new class of PEG derivative interferon alpha. The advantage it has is, instead of having two linear

PEG molecules at two different sites, it achieves the same effect by attachment of two linear PEG molecules at a single site. Therefore, the attached PEG mass is double without having multiple sites of pegylation. The complete specification then speaks of the advantages of this conjugate over the unmodified IFN alpha (IFN alpha without a PEG attached) for, it is an unconjugated IFN alpha. It also states that this conjugate, when compared to other PEG interferon alpha conjugates has (i) a much greater antiproliferative activity, (ii) disproportionate to the enhancement or reduction that occurs in its other characteristics and (iii) virtually no immunogenicity. It is repeated in the complete specification that the antiproliferative activity against tumor cells and antiviral activity against cells infected with a virus are the known activities of the interferonα.

OBVIOUSNESS

28. Every examination report has cited the prior art Monfardini as rendering the invention obvious. This is cited as a prior art even in the complete specification and it is referred to in various articles submitted by the parties and therefore, there is no escape from dealing with this and we have to address this issue of obviousness with reference to Monfardini and see whether the patent withstands the Monfardini test.

29. Before dealing with Monfardini, we shall look at other prior arts which were referred to during the course of arguments. One is Ex.A, 472 Patent. Its priority date is 23.5.1990. This shows that PEG derivatives are useful as protein modifiers of interferons and the protein thus modified

has minimized antigenicity, prolonged plasma half-life. This prior art shows that there is a danger that immune reaction might be caused when physiologically active protein obtained from the heterologous organism is administered to humans and in order to solve the problem, it was attempted to chemically modify the physiologically active protein with an artificial high molecular compound by using PEG. It talked about various methods of chemically binding PEGged protein. Formula-IV in this prior art represents the modified protein of that prior art.The alkyl group shown as R could be an alkyl group having 1 to 8 carbon atoms Of these the lower alkyl groups are preferred namely those having 1 to 4 carbon atoms the most preferred being methyl. **Claim 1 of the present invention says that R and R' are independently lower alkyl and Claim 4 is for " A conjugate of claim 1 where R and R' are methyl.** The specification says **R and R' may be any lower alkyl by which it means an alkyl group having 1 to 6 carbon atoms. like methyl, ethyl, isopropyl etc. and that the preferred one is methyl**. This prior art says that the protein could be any protein derived from animals which includes interferons. Several examples were given, as many as 72 examples. Example 20 is PEG-2 modified human interferonα.

30. The next prior art is of the year 1993 (Exhibit B), viz., "Distribution and Tissue Uptake of Poly (ethylene glycol) with Different Molecular Weights after Intravenous Administration to Mice". The abstract shows **that the terminal half-life of PEG in the circulation extended has the PEG molecular weight increased**. This article refers to studies which demonstrated **that PEG modification was effective in prolonging the**

half-life of drugs, changing the body distribution of drugs, protecting the drug from the attack of proteases as well as antibodies and reducing the antigenicity of drugs and it is one of the useful strategies to modify the pattern of drug distribution for possible improvement in therapeutic efficacy and reduction in side effects of the drug. "In conclusion, the molecular weight of PEG greatly affected the time profile of PEG circulation in the blood and hence, the organ accumulation. Considering the body fate of PEG-modified drugs in vivo, PEG of ~50000 molecular weight will exhibit a long half-life in the circulation with a low organ accumulation compared with PEG of other molecular weights, provided each drug molecule carries only one PEG chain". This was pointed out by the respondent to show that it talked of linear conjugate proteins and therefore, this prior art may actually discourage the inventor from trying branched conjugates with 50000 molecular weight.

31. Exhibit-C is "Preparation of long-acting superoxide dismutase using high molecular weight polyethylene glycol (41000-72000 daltons)". This was relied on to show how superoxide dismutase when pegylated retains 90% to 100% of SOD activity of the native enzyme, but demonstrated longer persistence and lower immunogenicity and antigenicity. Originally the abstract alone was filed and at the time of the appeal the entire document was produced along with M.P.111/2012. The respondent objected to the belated production. This prior art is referred to in Monfardini . Monfardini is referred in the specifications. So, surely the inventor had the benefit of the teachings of this document. We surely must see if this document is relevant for deciding obviousness. In fact, it speaks

of the advantages the PEGylation has on therapeutical applications, especially branched pegylation.

32. Exhibit-D is a PCT Application" Non-Antigenic Branched Polymer Conjugates" This is actually subsequent to Monfardini. Therefore, according to the respondent, this would show that even after Monfardini, there was no encouragement to branched conjugates. This invention relates to branched polymers which are useful in extending the in vivo circulating life of biologically active materials. "Excessive polymer conjugation and/or conjugation involving a therapeutic moiety's active site where groups associated with bioactivity are found, however, often result in loss of activity and thus therapeutic usefulness". One suggestion for overcoming the problems discussed above is to use longer, higher molecular weight polymers. The other aspects of this invention are conjugates containing biologically active materials and one or more of the branched polymers. It specifically mentioned that the biologically active materials include proteins, peptides, enzymes, medicinal chemicals or organic moieties whether synthesized or isolated from nature. It speaks of chief advantage of branching of the polymers that imparts an umbrella-like three-dimensional protective covering to the materials. It says that all the desired properties of polymer conjugation are realized and loss of bioactivity is minimized. The second advantage of the branched polymer is that the benefit associated with attaching several strands of polymers to a bioeffecting material was obtained but actually substantially fewer conjugation sites were required. According to the respondent, since the interferon has 11 available sites, it is very unlikely that they would have

conjugated interferon in that manner. This invention also says that the molecular weights of about 5000 daltons are most preferred. According to the respondent, the question is would anyone try pegylating with molecular weight of 40000 daltons, when that invention had specifically stated that it is well-suited for compounds which have few or a single nucleophilic attachment site for polymer conjugation. Therefore, according to the respondent even after Monfardini, the inventors were not encouraged to branch a protein which has many attachment sites. This prior art refers to 5000 daltons in the context of molecular weight of each PEG chain , within a range between 200 and 12000 daltons. It also says that for multiple branched polymers the MW should not exceed 80,000 Daltons. **So this prior art is not really a deterrent**. In the Invention each chain has a MW of 20,000 daltons totalling to the preferred weight of 40,000 daltons. Claim 1. Speaks of 26,000 -66,000 daltons, Claim 2 speaks of 35,000 -45,000 daltons and claim 3 of 40,000 daltons. This prior art prefers an alkyl group of 1-10 carbon atoms and refers to interferons among the biologically active materials suitable for conjugation. This prior art is stated to be" particularly suitable for compounds which have few or single attachment sites" but this is not teaching away. When one wants to multiply the chains and there are fewer attachment sites, branching helps. But, that does not mean that branching is not to be done for proteins which have more number of attachment sites.

33. Now, we come to Monfardini. As we have observed earlier, the examination reports cited Monfardini as destroying novelty as well as rendering the patent obvious. Monfardini was filed before the Controller

as Exhibit-E. Exhibit-E was filed by the first opponent, M/s.WOCKHARDT LTD., which is not a party here, as REP-4 and the Controller has stated that whatever he has discussed in the other opposition proceedings will apply to the appellant's opposition. The Controller has stated that while he agrees that both the formulae filed as REP-4 and Formula-I of the patent in question are similar, but not identical. According to the Controller, they are not identical because in Formula-VI (REP-4) a protein is bonded to –NH- whereas in Formula-I of the patent in question IFN alpha is bonded to –NH- or –O-. He has rejected Monfardini as a prior art which destroys obviousness on the ground that Monfardini discussed enzymes and enzymes are different from interferon. On this ground, the Controller had concluded that Monfardini does not make the patent obvious. The Opposition Board had observed that a skilled person would have " *think (sic) of branched PEG interferon alpha conjugates having a molecular weight of around 40000 daltons by going through Exhibit-E which disclosed branched PEG with proteins.*" After going through all the documents, the Controller came to the following conclusions:

(1) Interferons are known and known to be bifunctional.

(2) Preparation of PEG conjugates is known.

(3) Effects of conjugation are known.

(4) Variation of tissue uptake and distribution with variance in molecular weight is known.

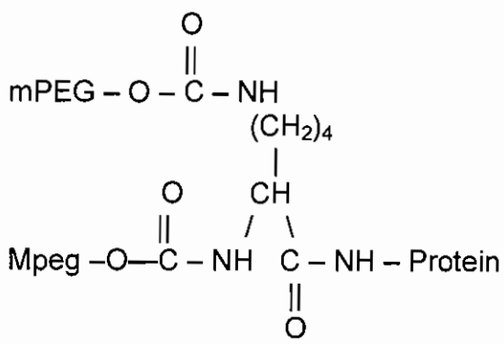
(5) Effects on urinary clearance and liver clearance due to variance in molecular weights of the conjugates are known.

Therefore, all these are known.

34. The abstract in Monfardini shows that the procedures are described for linking monomethozypoly (ethylene glycol) (mPEG) to both € and α amino groups of lysine and the lysine carboxyl group can then be activated as a succinimidyl ester to obtain a new mPEG derivative. The authors of Monfardini have carried out a comparison of mPEG and mPEG-2-modified enzymes. This document recognizes differences such as, rapid clearance from circulation when peptides and proteins are used as therapeutic agents and they say that linking suitable hydrophilic or amphiphilic polymers to peptides and proteins overcomes this problem because, polymer cloud surrounding the protein increases stability towards proteolysis and reduces renal excretion and immunological complications. mPEG was the polymer most used for these applications with linear polymers of molecular weights in the range of 2000 – 5000 being preferred, but it shows that high molecular weight mPEGs and branched mPEG were also used. It refers to the work of Somak et al (Ex-C) to show the utility of high molecular weight mPEG for protein modification. "*In view of the great utility of large or branched monofunctional PEGs for increasing the polymer cloud volume surrounding a protein while maintaining the same number of binding sites, we have prepared a new branched mPEG derivative devoid of the above disadvantages. This derivative also presents the important advantage of easy analytical characterization of the adduct. This new polymer preparation is based on direct linkage of mPEGs to the α and € amino groups of lysine (to give mPEG2—COOH), followed by activation of the carboxyl group as the succinimidyl ester (to give mPEG2 – COOSU) Figure-1. This paper reports the use of this new derivative and reports the*

comparison of the properties of proteins modified with linear and branched mPEGs". The structure VI of the Figure-1 is reproduced here below.

VI. NH_2 – protein



VI

It may be compared with the Formula given in the specification as extracted earlier. They are identical where instead of 'X' in the complete specification, this prior art has used the word, 'NH'. Now, in the complete specification which was extracted above, it is seen that 'X' could be 'NH' or 'O', and the Claims say that NH is preferred. **Therefore, the Controller erred in citing this as a difference**. Where the complete specification uses the term 'interferon α', this prior art uses the word, 'protein'. Interferon is one kind of protein and this prior art says that this is generally applicable to PEG chemistry. **The Controller again erred in citing this as a difference** .This paper also refers to the molecular weight of 40000 daltons. It reports the comparison of properties of enzymes modified by linear and branched polymers and it has chosen four enzymes, ribonuclease, catalase, asparaginase and trypsin. Insofar as ribonuclease is concerned, it showed that the protection offered by branched mPEG2 is more effective than linear mPEG. Similar positive results were obtained

with asparaginase and trypsin also. The results reported in this paper demonstrate that new, branched mPEG dimers may be prepared by a "two step" procedure, using mPEG p-nitrophenyl carbonate or by a "single-step" procedure, using more reactive mPEG succinimidyl carbonate. The branched polymer, activated as the succinimidyl ester (mPEG2 – COOSu), reacts under mild aqueous conditions, compatible with the stability of most enzymes, to give a stable amide linkage with protein amino groups.

35. This report says that

> *"though branched mPEG2 was studied for its utility in enzyme modification, it has a general applicability in several areas of PEG chemistry". .... "Preliminary data obtained in our laboratory suggest improved immunological properties as well as increased mPEG conjugates. The pharmacokinetics and immunological behaviour of enzymes of potential therapeutic interest, as well as the effect on solubility and activity in organic solvents, are under active investigation and will be reported soon."*

The last paragraph of the report extracted above was read out by the learned counsel for the respondent to show that there was nothing conclusive about the report, and that the success of pegylating interferon was not assured by this prior art and therefore, this prior art cannot be cited as destroying non-obviousness. We do not think that this prior art is discouraging research along the same lines on the other hand, it clearly keeps the door wide open.

36. Pending the appeal the respondent filed 3 documents, viz.,

Annexure A "Better by Design" by Dr.Graham R.Foster (to prove efficacy).

Annexure B "Pegylation, 'A Novel Process for Modifying Pharmacokinetics'" by J.Milton Harris and others.

Annexure C "Rational Design of a Potent Long Lasting Form of Interferon A 40KD a Branched Polyethylene Glycol-Conjugated Interferon α-2a for the treatment of Hepatitis C by Pascal Bailon and others (to prove efficacy)

All these documents are after the priority date. We will deal with Annexures A and C later when discussing S.3(d).

37. From Annexure B we see that pegylation was first developed by Davis, Abuchowski and colleagues in the 1970s. Their goal was to enhance the delivery of therapeutic molecules; perhaps more importantly, pegylation has also been shown to change the pharmacokinetics and thus, the pharmacodynamics of the therapeutic molecule without the limitations of classical liposomes. PEG moieties are inert, long-chain amphiphilic molecules produced by linking repeating units of ethylene oxide. Using pegylation to increase the size and molecular weight of a therapeutic protein alters the immunological, pharmacokinetic and pharmacodynamic properties of the protein in ways that can extend its potential uses. Large proteins generally have more attachment sites and therefore, are commonly multipegylated. Attachment at multiple sites, however, increases the likelihood of steric interference at the active site of the native protein, resulting in a possible inhibition or reduction of activity. The attachment of branched PEG moieties can increase the size of the moiety (and net total molecular weight of the conjugated protein) without a

resultant increase in the number of attachment sites. In addition, branched chain PEG conjugates have been shown to have increased pH and thermal stability and increased resistance to proteolytic digestion compared with linear PEG conjugates. The authors cited from Monfardini to show the advantage of branched chain PEG conjugates. They also said that pegylation may decrease the cellular protein clearance.

38. We refer to the judgment of the United States Court of Appeals for the Federal Circuit in Pfizer, Inc. v. Apotex, Inc. in 2006-1261 dated 22.3.2007. Apotex had the generic version of Pfizer's Norvasc. It contains amlodipine besylate. The active ingredient is commonly referred to amlodipine. These active drug molecules are made into pharmaceutically acceptable acid addition salts to improve their bioavailability. Amlodipine besylate is an acid addition salt form of amlodipine formed from the reaction of amlodipine. They had also developed another besylate salt, amlodipine maleate which according to Pfizer was bioequivalent. The examiner referred to two prior arts one of them disclosed aryl sulphonic acid salts which include besylate. Finally, the patent was granted and it was launched as a commercial product. Then, Apotex prayed for declaratory judgment that the patent was invalid for anticipation and obviousness. There was another prior art which is an article "Pharmaceutical Salts" by Berge. The contention that there is no reliable way of predicting the influence of a particular salt species on the behaviour of a parent compound was accepted. The Court proceeded with the presumption of the validity of patent which was statutorily infringed there, called upon Apotex to discharge the statutory burden.

Before the Court, the parties did not dispute that benzene sulphonate was known. The prior art elicited a genus of pharmaceutically acceptable anions such as the hydrochloride, hydrobromide, sulphate, phosphate or acide phosphate, acetate, maleate, fumarate, lactate, tartrate, citrate and gluconate. This prior art only disclosed maleate action as an addition of salts of amlodipine. It did not expressly disclose amlodipine besylate. The Court of Appeals observed that neither they did exclude amlodipine besylate or the benzene sulphonate anion. Therefore, '909 patent claims were held to literally encompass amlodipine besylate. The Court held that "*a suggestion, teaching or motivation to combine the relevant prior art teachings to achieve the claimed invention does not have to be found explicitly in the prior art references sought to be combined, but rather 'may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself'*. However, irrefutable evidence showed that a skilled chemist at the time would simply make known pharmaceutically-acceptable salts of whatever active ingredient with which he or she was working at the time. Pfizer had admitted prior art documents which disclosed the use of benzene sulphonate for improving the bioavailability of other pharmaceuticals. The Court said this is *"therefore highly relevant in weighing the factors relating to obviousness.* " The District Court had held in that case that the invention was non-obvious because in 1986, it was generally unpredictable as to whether a particular salt would form and what its exact properties would be. The Court of Appeal held that this finding is correct, but the conclusion flowed from the factual finding is not correct. The Court held that "o**bviousness cannot be avoided simply by showing of some**

degree of unpredictability in the art so long as there was a reasonable probability of success. The Court held that indeed, **a rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt – including those specifically listed in the '909 patent itself – would be separately patentable, simply because the formation and properties of each salt must be verified through testing.** This cannot be the proper standard "**since the expectation of success need only be reasonable, not absolute.** *We also note that the 909 patent placed no limitations on the acid addition salt whatsoever, except that it be non-toxic and formed from an acid containing a pharmaceutically-acceptable anion. Thus, although Dr.Wells testified that it was not guaranteed whether amlodipine besylate would form and what its salient characteristics would be "this does not overcome (the prior art's) teaching that [amlodipine besylate] will work" Corkill. 771F.2d at1500. Considering all of the evidence, we conclude that the district court clearly erred in finding that Apotex failed to produce clear and convincing evidence that one skilled in the art would have had a reasonable expectation of success with the besylate salt of amlodipine.*" This conclusion on obviousness appears to be almost tailor-made for this case. Here too, the prior arts while not experimenting with interferon specifically did not exclude it, the success of Ex-C and Ex-E would have given the person skilled in the art a reasonable hope of success. All the claim paradigms were mentioned in the prior arts. The unpredictability of success cannot rule out obviousness. So even if different proteins may display different properties, the expectation of success was reasonable

especially since it was known that linear pegylation improved the activity of Interferon.

39. In KSR International Co. v. Teleflex Inc. Et.al (No.04-1350, decided on 30.4.2007), the United States Court of Appeals for the Federal Circuit refixed the bar on patentability. That case revolved around the question of obviousness and stated that the Court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. It stated that the question is not as to the combination of obviousness of the patent but as to the combination of obviousness of a person of ordinary skill in the art. It stated that the *"Court for seeing obviousness need not seek out precise teaching, but it can consider the inferences and creative steps that a person of ordinary skill in the art would employ. The Court erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and their are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Finally, the court drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. Rigid preventative rules that deny recourse to common sense are neither necessary under, nor consistent with, this court's case law. "*

40. This case refers to hindsight which is relevant for us to decide the case. While deciding the case we constantly asked ourselves if we were guided by hindsight rather than actual assessment of what was obvious on the relevant date and what was not innovative and what a person skilled in the art would try, for this invention has obtained a patent. While the Indian law does not create a statutory presumption of validity of the patent, we must be loath to set aside the grant, as hindsight bias is a trap into which one might easily fall and thereby deny to a deserving inventor the fruits of the invention. .

41. Monfardini deals with branched PEG protein in general and the PEG actvitiy of enzymes in particular. Even as per the Monfardini examples, we see the activity modification on the enzymes because of pegylation and the structure-VI in Figure-I of the paper. The advantage of branched PEGs for increasing polymer cloud surrounding is learnt from Monfardini. Monfardini which is admittedly a prior art has acknowledged that Somack et al had recommended high MWPEg for protein modification. Then the inventor cannot deny that the person skilled in the art would have known the utility of using high molecular weight while PEGylating, he would not have thought that this was restricted to enzymes alone or only to Superoxide dismutase. The utility of high molecular weight for protein modification is in the prior art. The comparison of the properties of the linear conjugated protein and branched conjugated protein was before the persons involved in the art. The fact that out of 4 enzymes, Monfardini found positive results in three enzymes is only an encouraging factor for the person skilled in the art. Monfardini shows that

branched mPEG dimers may be prepared either by a two step or single-step procedure. The complete specification disclosed that the inventor has used only a conventional method to obtain interferon α. The conjugate of Formula-I was produced by forming a reagent which is an N-hydroxy succinimide ester derivative of PEG which is stated in Monfardini.

42. The non-obviousness and novelty factors are sometimes sitting there cheek–by-jowl, "The Law of Patents" by Nard second Edition says that Novelty "*seeks to assure the public domain remains undisturbed*" while non–obviousness "*demands that the claimed invention be sufficiently removed from the prior art*". This text also says that non-obvious enquiry is "*a more aggressive sentry*" and "*a richer policy tool that allows for the combination of prior art references and demands more complex rules.*" In KSR, the US Supreme Court held that the analysis of obviousness must be made explicit, and the reasoning to support the conclusion of obviousness must be articulated with rational underpinnings, the Court may have to look at the inter-related teachings of the multiple patents, the effect of demands known to the design community and the background knowledge possessed by a person having ordinary skill in the art. So the determination on obviousness is a legal one. The Court has to see a) what is the prior art b) the differences between the prior art and the invention and c) the skill of the imaginary ordinary man. This man has skill but until KSR came along he had no inventive or creative capacity. Such a person is hard to find, but we had to conjure this man in our mind as we do the man on the Clapham omnibus. By way of diversion, it seems he is referred by the acronym Mr.PHOSITA or just PHOSITA, the

preferred acronym could be POSIT it sounds better or POSITA if you please. Getting back to the track, as KSR says this man is *"A person of ordinary skill is also a person of ordinary creativity not an automaton."* So an automaton- like unimaginative but skilled man has now been allowed to have a modicum of creativity and imagination by the grace of the U.S.Supreme Court! We must remember that this ordinary man has skill in this art. He is not ignorant of its basics, nor is he ignorant of the activities in the particular field. He is also not ignorant of the demand on this art. "He is just an average man..... Well... just an ordinary man." But he is no dullard . He has read the prior art and knows how to proceed in the normal course of research with what he knows of the state of the art. He does not need to by guided along step by step. He can work his way through. He reads the prior arts as a whole and allows himself to be taught by what is contained therein. He is neither picking out the" teaching towards passages" like the challenger, nor is he seeking out the "teaching away passages" like the defender. In this case he is a person familiar with or engaged in pEG chemistry. He knew that it was a time of intense activity in this field of chemistry. The person defending the patent will undoubtedly inform the Court that there was nothing in the prior art to encourage the person skilled in the art to work toward the invention. KSR says "The question is not whether the combination was obvious to the patentee but whether the combination was obvious to the person skilled in the art. Under the correct analysis, any need or problem known in the field of endeavour at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." And one of the easy ways by which "a patent's subject matter can be proved

obvious is by noting that there was an obvious solution encompassed by the patent's claims." KSR also says that if pursuit of known options within the technical grasp of the person skilled art leads to the anticipated success " it is likely the product not of innovation but of ordinary skill and common sense".

43. Once the Court has the facts it has to put the clock back to the date of the invention and see if this ordinary man would have found it obvious to put this invention together. In the present case, Interferon had already been used to treat hepatitis C. There were problems in the use of this protein as such. PEGylation was known from 1970s. Pegylation of proteins was known to improve the activity of the proteins. There was intense activity in the field of PEG chemistry and the person skilled in the art will be acquainted with it, if not directly involved in it. Linear conjugates of Protein showed improvement over unconjugated protein. Monfardini said that when Pegylated, branched conjugates of enzymes showed a marked improvement over linear conjugates of enzyme. Monfardini showed the structure of such branched conjugates positioning the PEG chains, the amide bond and the protein in a particular sequence. Monfardini said that though this paper referred to experiments with enzymes it was applicable to PEG chemistry in general; it worked with a molecular weight of 40,000 daltons. All that is missing in Monfardini is the specific mention of Interferon in the structure. Structural similarity is a prima facie evidence of obviousness. Here it is more than structural similarity. Monfardini tells us of the use of NH, the invention uses X which could be NH or O, NH being preferred. And as observed earlier, the word

protein in Monfardini is replaced by Interferon which is a protein. The Person of Skill In The art takes a look at Monfardini and also at the other exhibits. He knows that the activity of Interferon has to be improved for Hepatitis C cases. He knows that linear pegylation will improve it a bit. He knows that branched pegylation has shown marked improvement over linear conjugates in the case of superoxide dismutase and three enzymes. He is confident that branched PEGylation of Interferon will work; it has worked in Monfardini with enzymes. Monfardini gives him the structure on a platter. He also knows that he can work with molecular weight range of 5000-40,000 daltons to strike oil. He has reason to believe that higher may be better. Why would POSIT not be willing to make trial and error experiments and see if it works as *Synthon* said?

44. The structure VI in Figure 1 of Monfardini is the same as the claimed structure, but for two differences which are not really differences.

- In a preferred conjugate, the amide bond is NH which is stated in structure VI in Figure-I of the Monfardini. So the fact that claim1 says X is NH or O is not relevant.
- The substitution of IFN in the place of protein in the Monfardini structure is an obvious substitution for Monfardini does not exclude IFN, and further Monfardini indicates wider application and does not restrict the Pegylation advantages to enzymes alone.
- Not just Monfardini, but the other prior arts also indicate that there are advantages in using a higher molecular weight. And Monfardini mentions 40,000 daltons which is the claimed preference.
- It was known that the conjugated interferon would result in enhancement of its activity. It was also known that the branched conjugation was better than the linear conjugation.

- Monfardini also speaks of general applicability in PEG chemistry and further, in fact, it makes it clear that this report has used a new derivative for protein but has evaluated the degree of enzyme modification. This does not mean that for enzymes other than those which were evaluated or for Proteins other than enzymes, this branched pegylation will not work.
- Exhibit A speaks of using lower alkyl group for Pegylation.
- Ex.B says that PEG modification has several advantages. we have already referred to this prior art.
- Ex C is referred in Monfardini as encouraging use of high molecular weight.

So these materials provided the knowledge to the person skilled in the art regarding the advantages of branched PEGylation of IFN. He would use the conventional methods as did the inventor. If the methods used are conventional, there is no difficulty in the methods. Even if one grants a degree of unpredictability in the behavior of interferon there was a greater reason to expect success since IFn had responded positively to linear conjugation. The Skilled person would have seen the structure from Formula VI in Monfardini. He knows that it is likely to succeed since with enzymes there was a three out of four success. There is nothing to discourage him from investigating the effect on Interferon from what he learnt from Monfardini and others; he also knows that even Monfardini intends further investigation and trial. Monfardini worked on branch pegylating enzymes, encouraged by Somack et al. Monfardini itself tells us, what was the level of skill on that date. "The ultimate judgment of obviousness is a legal determination'(KSR) and "The combination of familiar elements according to known methods is likely to be obvious when

it does no more than yield predictable results." (KSR). In this case, we have seen what is known, we have seen that only conventional methods were used and apart from referring to the results as "surprising", the inventor does not say why it was surprising, since the previous sentence in the Complete Specification reads;" It has been now observed that in the case of interferon, PEGylation reduces in vitro antiviral activity but increases antiproliferative activity in human tumor cells." If the results were predictable then there is no surprise. Definitely the prior arts abovementioned and in particular ,Monfardini render **the invention obvious**.

Objection under S.3 (d) of the Patents Act:

45. We will now take up section 3(d) objection. According to the appellant, the burden of proof that the patent does not fall under section 3(d) is squarely on the patentee. It is enough if the appellant shows that the invention is the same substance. In the opposition, the appellant had stated that both interferon alpha and PEG conjugate were known substances as on the priority date. Therefore, whether it is a new form of known interferon alpha or a new form of PEG conjugate, the patentee must demonstrate the enhancement of the known efficacy. The opposition stated that the applicant had produced no evidence to show how this new form results in the enhancement of its known efficacy; rather it merely disclosed that the new form has properties that have no difference from the known PEG conjugate. As regards 3(d), the appellant's main objection was that the respondent has not shown that there is any enhancement of the known efficacy of the linear Monfardini

PEG conjugate. According to the respondent, the compound can be construed to be a new form of known substance when the new form is directly derived from the known substance. Since in the present case, the branched PEG IFN conjugate is directly derived from the unmodified interferon alpha and not from the linear PEG interferon alpha conjugate, it is sufficient if the respondent shows that the branched PEG IFN alpha conjugate has enhanced efficacy compared to the known efficacy of the unmodified interferon alpha. According to the respondent, Example-3 and Example-6 clearly show increase in vitro antiproliferative activity and in vivo antiproliferative activity and significant reduction in tumor cells. According to the respondent, the conjugate is a product which is protein by pegylating a polymer such as PEG derivative with biological molecule like a protein and when Monfardini disclosed only PEG conjugates of four enzymes, Monfardini conjugates cannot be a known substance for the purpose of section 3(d) of the Act. According to the respondent, the Controller has correctly held that the known compound is the unmodified IFN alpha and the data provided in the specification proves enhanced therapeutic efficacy of the branched PEG interferon conjugates which is the present invention. He distinguished Novartis case, cited supra, by saying that in the Novartis case, the known substance for beta crystal form of imatinib mesylate will be imatinib mesylate and not imatinib base and the comparison between beta crystal form and imatinib mesylate was not sufficient to prove 3(d) requirement. According to the appellant, Ex-A and Ex-C, the articles by Harris and Bailon must be taken on record for the comparative data provided between linear and branched PEG interferon alpha conjugates. The author of Ex-C Bailon is the inventor.

46. The problem here arises because of the words used in the complete specification that the invention "is a new class of PEG derivative of interferon". Therefore, it is the respondent's own case that this is a new form of PEG derivative of interferon. Further, in the complete specification it is also stated that the branched PEG is the attachment of two linear PEGs at a single site. The complete specification repeatedly talks of the increased efficacy of this class of pegylated interferon alpha over other PEG interferon alpha conjugates. This claim is not made just once, but over and over again. If as is claimed by the patentee in the complete specification, this is a new form of PEG derivative interferon and has superior activity over other PEG interferon alpha conjugates, then it is for the patentee to prove that. The Hon'ble High Court in the Novartis case (cited supra) had held that it is the patentee's duty to prove S.3 (d) efficacy Annexures A and C filed pending appeal (referred to above) are after the priority date. They give a comparative data of unmodified interferon linear PEG as 5 KD, linear PEG as 12 KD and branched PEG as 40 KD. This only shows that the patentee tacitly admits that it should have shown the significant difference with regard to the efficacy between known substance which as per the complete specification is the PEG derivatives of interferon and the new form of PEG derivatives of interferon.

47. It was known that PEG conjugated biomolecules have (i) better physical and thermal stability, (ii) protection against susceptibility to enzymatic degradation, (iii) increased solubility, (iv) longer in vivo circulating half-life, (v) decreased clearance and (vi) enhancing potency.

It was also known at the time of invention that branched PEG conjugates had increased pH and thermal stability and greater stability than linear PEG conjugates and reduced immunogenicity and antigenicity and reduced toxicity. It was also known that pegylation of some proteins may result in reduction of in vitro activity along with the enhanced in vivo activity and that the pegylation of interferon reduces in vitro antiviral activity but increases antiproliferative activity in human tumor cells. The specification says, "this invention has surprising properties i.e., its antiproliferative activity is much higher than that not only of interferon but of other PEG interferon conjugates as well. Though the antiproliferative activity is more increased, the reduction in antiviral activity is the same. Further, according to the inventor, this invention has virtually no antibody formation, while other PEG interferon alpha conjugates elicited limited antibody formation". For these comparisons with other PEG interferon conjugates, there are no examples in the specifications.

48. The Controller says that the enhancement in the activity has shown to be related to the "molecular weight chosen by the patentee. In other words a conjugate having the molecular weight falling outside this specified range does not show enhancement and probably this inference leads to the idea that a mere pegylation of interferon will not lead to the objects of the patentee." "Probably" is not the word we should choose for deciding efficacy. The efficacy should be proved with certainty.

49. Next he says "that the patentee has proved efficacy by comparing with either"unconjugated interferon or PEG interferonα 2B (12KD) and

probably with other conjugates of lower MW." Again it is"probably". He is perhaps referring to Annexures A & C which were produced with the reply statement, but not as 'evidence'.

50. The specifications show experiments only with the unconjugated IFN, though this invention is said to be superior to the other conjugates and linear conjugates. F**or this we have no contemporaneous intrinsic or extrinsic evidence**. The examples in the Complete Specification show improvement over unconjugated interferon, but the inventor claims surprising activity when compared to other conjugated interferon which is not shown. Hence the evidence for the "surprising activity " is not adequate. Annexures A and C are without the supporting affidavits of the authors. The authors must present themselves as witnesses either in person or through proof affidavits for only then the evidence can be admitted. They are also documents published after the priority date .We have already held against the respondent on obviousness. With regards to S.3(d), we find that the respondent has not discharged the burden of proof.

NOVELTY

51. To defeat novelty, the appellant should show that an earlier document , disclosed all that the patentee is seeking to patent. And that each limitation of the claimed invention is found in a single prior art reference. The appellant has not done this. **So the attack on novelty is rejected.**

52. The Controller and the Opposition Board must bear in mind that their orders and recommendations must have clarity. They need not be lengthy, but they must be self-contained, speaking orders. While referring to documents, it is better to describe the documents fully at least once. For example, "Ex –C [Preparation of long-acting superoxide dismutase using high molecular weight polyethylene glycol (41000-72000 daltons) (Somack et. Al)]", instead of baldly referring to the exhibits as REP-3 or REP-4 without saying what they are even once in the order. This will help a great deal when the matter comes up in appeal before this Board or goes before the High Court. The Controller is admittedly not bound by the recommendations. He has to decide the case independently. But the recommendations are before him. If he differs, it is always advisable to spell out clearly the reasons for difference. In OA/4/2009/PT/CH [M/s Diamcad N.V. and another vs Asst. Controller of Patents and Designs, Chennai and another} by its order dated 3rd August 2012, this Board had held that the report of the Opposition board shall be furnished to the parties before the hearing in the interest of fairness. So the parties must know the reasons why the Controller agrees or disagrees with the Board of experts. Having a list of the documents in front, will help for the the order can avoid the mistake of straying into documents not marked. No order can presume to be infallible but to a great extent errors can be minimized. These are just by way of pointers of guidance.