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Bezeichnung der Erfindung:
Title of invention:
Titre de l'invention : DNA sequences, recombinant DNA molecules and processes for producing interferon-alpha like polypeptides.

Klassifikation / Classification / Classement :

ENTSCHEIDUNG / DECISION

vom / of / du 16 February 1989

Anmelder / Applicant / Demandeur :

Patentinhaber / Proprietor of the patent / Titulaire du brevet : Biogen N.V.

Einsprechender / Opponent / Opposant :
01 Hoffmann-La Roche & Co AG
02 The Upjohn Company
03 Boehringer Ingelheim Zen.GmbH
04 Bender & Co Ges mbH
05 Cetus Corporation
06 Hoechst AG
07 Boehringer Mannheim GmbH
08 Ciba-Geigy AG
09 Boehringer Ingelheim Pharma Ges mbH

Stichwort / Headword / Référence : Alpha-interferons/BIOGEN

EPÜ / EPC / CBE : Articles 54, 56, 83, 84, 87 to 89, 102 and Rule 28
Paris Convention Articles 4B and 4F

Schlagwort / Keyword / Mot clé : "Opposition grounds - Matters arising from amendments"

"Sufficiency - Reliability for obtaining members of a claimed class"
"Novelty - Gene bank"
"Priority - Entity and component part of it"
"Priority & inventive step - Subsequent publication of the content of a priority application not state of the art against European application - Applicability of the Paris Convention".

Leitsatz/Headnote/Sommaire

I. When amendments are made to a patent during an opposition, Article 102(3) EPC requires consideration as to whether the amendments introduce any contravention of any requirement of the Convention, including Article 84 EPC; Article 102(3) EPC does not allow objections to be based upon Article 84 EPC, if such objections do not arise out of the amendments made.
(further to T 227/88, dated 15 December 1988)
(cf. point 3.7 of the reasons)

.../...

II. Variations in the construction within a class of genetic precursors, such as recombinant DNA molecules, claimed by a combination of structural limitations and functional tests are immaterial to the sufficiency of the disclosure provided the skilled person could obtain reliably members of the class without necessarily knowing in advance which member would thereby be made available (further to T 281/86 dated 27 January 1988) (cf. Point 4.5 of the reasons).

III. If an entity itself is disclosed to the skilled person, this does not necessarily mean that a component part is also disclosed for the purpose of priority if this is not envisaged directly and unambiguously as such, and requires considerable investigation to reveal its identity (cf. Point 6.3 of the reasons).

IV. When priority is claimed for a European patent application, the publication of the content of the priority application, in the interval between the filing of that application and the filing of the (final) European patent application cannot be used as state of the art against any claim in the latter application. However, if such publication goes beyond the content of a previously filed application and includes subject-matters not covered by the disclosure of that application, such disclosure may in principle be cited against any claim in the (final) European patent application relying on a priority date subsequent to the publication date (cf. Point 7.8 of the reasons).

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number : T 301/87 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 16 February 1989

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Decision under appeal : Decision of Opposition Division of the European Patent Office dated 10 June 1987 revoking European patent No. 0 032 134 pursuant to Article 102(1) EPC.

Composition of the Board :

Chairman : P. Lançon

Members : G. Szabo
D. Holzner
Co-rapporteurs
G. Paterson
E. Persson

Summary of Facts and Submissions

I. European patent No. 32 134 was granted on 15 August 1984 with 34 claims for ten Contracting States and 23 claims for Austria, in response to European application No. 81 300 050.2. The priority of three earlier applications was claimed, namely of 8 January 1980 (BIOGEN I), 3 April 1980 (BIOGEN II) and 2 October 1980 (BIOGEN III). Claims 1, 2, 3 and 6 were as follows:

1. A recombinant DNA molecule for use in cloning a DNA sequence in bacteria, yeasts or animals cells, said recombinant DNA molecule comprising a DNA sequence selected from:

(a) the DNA inserts of Z-pBR322(Pst)/HcIF-4c, Z-pBR322(Pst)/HcIF-2h, Z-pBR322(Pst)/HcIF-SN35, Z-pBR322(Pst)/HcIF-SN42 and Z-pKT287 (Pst)/HcIF-2h-AH6, said DNA inserts being exemplified, but not limited to, the DNA inserts of the recombinant DNA molecules carried by the microorganisms identified by accession numbers DSM 1699-1703, respectively,

(b) DNA sequences which hybridise to any of the foregoing DNA inserts and which code for a polypeptide of the IFN-α type, and

(c) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences and inserts defined in (a) and (b) and which code for a polypeptide of the IFN-α type.

2. A recombinant DNA molecule according to claim 1, wherein said DNA sequence (b) which hybridises to said DNA insert (a) is selected from:

(d) the DNA inserts of Z-pBR322(Pst)/HcIF-II-206 and Z-pBR322(Pst)/HcIF-SN35-AHL6, said DNA inserts being exemplified, but not limited to, the DNA inserts of the recombinant DNA molecules carried by the microorganisms identified by accession numbers ATCC 31633-31634, respectively,

(e) DNA sequences which hybridise to any of the foregoing DNA inserts and which code for a polypeptide of the IFN-α type, and

(f) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences and inserts defined in (d) and (e) and which code for a polypeptide of the IFN-α type.

3. A recombinant DNA molecule according to Claim 1 or 2, wherein said DNA sequence (b) or (e) which hybridises to said DNA insert (a) or (d) is selected from:

(g) the hybridising portions of chromosomal DNA segments Hif-chr1, Hif-chr3, Hif-chr10-1, Hif-chr10-r, Hif-chr12, Hif-chr13, Hif-chr16-1, Hif-chr23, Hif-chr26, Hif-chr30 and Hif-chr35, said hybridising portions being exemplified, but not limited to, the DNA inserts of the recombinant DNA molecules carried by the microorganisms identified by accession numbers DSM 1914-1923 and ATCC 31760-31766, respectively,

(h) DNA sequences which hybridise to any of the foregoing DNA sequences and which code for a polypeptide of the IFN-α type, and

(i) DNA sequences which are degenerate as a result of the genetic code to the DNA sequences and inserts defined in (g) and (h) and which code for a polypeptide of the IFN-α type.

6. A recombinant DNA molecule according to any one of claims 1 to 4, wherein said DNA sequence is selected from DNA sequence of the formula:

TTACTGGTGGCCCTCCTGGTGCTCAGCTGCAAGTCAAGCTGC

TCTGTGGGCTGTGATCTGCCTCAAACCCACAGCCTGGGTAGCAGGAGGACCT

TGATGCTCCTGGCACAGATGAGGAGAATCTCTCTTTTCTCCTGCTTGAAGGA

TTACTGGTGGCCCTCCTGGTGCTCAGCTGCAAGTCAAGCTGC

TCTGTGGGCTGTGATCTGCCTCAAACCCACAGCCTGGGTAGCAGGAGGACCT

TGATGCTCCTGGCACAGATGAGGAGAATCTCTCTTTTCTCCTGCTTGAAGGA

CAGACATGACTTTGGATTTCCCCAGGAGGAGTTTGGCAACCAGTTCCAAAAG

GCTGAAACCATCCCTGTCCTCCATGAGATGATCCAGCAGATCTTCAATCTCT

TCAGCACAAAGGACTCATCTGCTGCTTGGGATGAGACCCTCCTAGACAAATT

CTACACTGAACTCTACCAGCAGCTGAATGACCTGGAAGCCTGTGTGATACAG

GGGGTGGGGGTGACAGAGACTCCCCTGATGAAGGAGGACTCCATTCTGGCTG

TGAGGAAATACTTCCAAAGAATCACTCTCTATCTGAAAGAGAAGAAATACAG

CCCTTGTGCCTGGGAGGTTGTCAGAGCAGAAATCATGAGATCTTTTTCTTTG

TCAACAAACTTGCAAGAAAGTTTAAGAAGTAAGGAA and TGTGATCTG

CCTCAAACCCACAGCCTGGGTAGCAGGAGGACCTTGATGCTCCTGGCACAGAT

GAGGAGAATCTCTCTTTTCTCCTGCTTGAAGGACAGACATGACTTTGGATTTC

CCCAGGAGGAGTTTGGCAACCAGTTCCAAAAGGCTGAAACCATCCCTGTCCTC

CATGAGATGATCCAGCAGATCTTCAATCTCTTCAGCACAAAGGACTCATCTGC

TGCTTGGGATGAGACCCTCCTAGACAAATTCTACACTGAACTCTACCAGCAGC

TGAATGACCTGGAAGCCTGTGTGATACAGGGGGTGGGGGTGACAGAGACTCCC

CTGATGAAGGAGGACTCCATTCTGGCTGTGAGGAAATACTTCCAAAGAATCAC

TCTCTATCTGAAAGAGAAGAAATACAGCCCTTGTGCCTGGGAGGTTGTCAGAG

CAGAAATCATGAGATCTTTTTCTTTGTCAACAAACTTGCAAGAAAGTTTAAGA

AGTAAGGAA.

II. Notices of Opposition were filed against the European patent by eight parties in the period from 18 August 1984 to 15 May 1985, and one Notice of Intervention, according to Article 105 EPC, was filed on 8 August 1985 (hereinafter referred to as Respondents I to IX). Revocation of the patent was requested on the grounds of Article 100(a), (b) and (c) EPC. During the procedure before the Opposition Division the following documents were, inter alia, cited:

(10), Zoon, K.C. et al, Proc. Natl. Acad. Sci. USA, 1979, 76, 5601-5605.

(16), Nagata, S., et al, Nature, 1980, 284, 316-320.

(21a), Streuli, M. et al, Science, 1980, 209, 1343-1347,

(93), Lawn, R.T. et al, Cell, 1978, 15, 1157-1174.

(108), Zoon et al, Abstract No. 32, referring to an oral disclosure at the Conference on Regulatory Functions on Interferons, New York 1979.

III. The Opposition Division revoked the patent in a decision on 10 December 1986, notified on 10 June 1987. The grounds were insufficiency, lack of clarity and support (Articles 83/100(b) and 84 EPC), lack of novelty and of inventive step (Article 100(a) EPC). As to Article 84 EPC, the Opposition Division considered that because the patentee had amended the claims, it had to examine in the circumstances whether or not the amended patent met all the requirements of the Convention, including Article 84 EPC.

(i) As to clarity, it was stated in the decision that the terms in Claim 1(b) and (c) such as "which hybridize", "a polypeptide of the IFN-α type" and "which are degenerate" were unclear and therefore unallowable in the patent. The tests relating to these terms did not give a clear guidance to the skilled person. In view of this, claims relying on them were unsupported, too broad and speculative with regard to the requirement of Article 84 EPC, and therefore covered subject-matter which was not sufficiently disclosed in the specification.

(ii) As regards sufficiency, the necessity to express the claimed DNA molecules for testing whether or not IFN-α type of polypeptides were provided, involved the use of microorganisms for expression. At the effective date, and this should be the priority date, only E. coli strains were available and other hosts became only ready for use at a later date.

Thus the reference to the use of the latter required further inventions and reduction to practice. The recombinant DNA molecules covered in Claim 1(b) were not, therefore, complying with Article 83 EPC.

(iii) The revocation of the patent by the first instance was also based on lack of novelty of Claims 1(b), 2(e), 3(h) and 8, in view of hybrid phages, which were contained in "Lawn's gene bank", a public collection of many fragments of fetal human chromosomes. It was stated that Claims 6, 20 and 33 were also anticipated by publication (21a), "Streuli", which had disclosed the subject-matter of such claims, since these could only derive priority from BIOGEN III (2.10.80).

(iv) As regards the inventive step, the Opposition Division confined itself to Claims 2(d) and 14, which relied on DNA containing specifically characterised and deposited fragments. Document (16), "Nagata", was published on 27 March 1980, before the priority date of these claims (BIOGEN II, 3.4.80) and revealed sequences which were structurally close enough to those claims to render them obvious in the absence of evidence showing unexpected improvements. The skilled person would have been successful in obtaining the claimed variants starting from the disclosure of document (16) by using standard methods, although the steps described in the same might not have been repeatable in all details.

The requests based on auxiliary sets of claims were also rejected on similar grounds as above.

IV. The Appellant (the Proprietor of the patent) filed an appeal against the decision on 2 August 1987 with the payment of the fee, and submitted a Statement of Grounds on 20 October 1987. Respondents I to VI, VIII and IX (being the corresponding Opponents and the Intervenant) filed various observations in the period from 13 February to 5 May 1988. After a Communication from the Board on 23 September 1988, the Appellant submitted replies and a new auxiliary set of claims on 23 December 1988 and further comments on 19 January 1989. Observations were received from Respondents VII (30.10.88) and VIII (19.1.89), and comments and experimental results from Respondents III, IV and IX (24.1.89 and 8.2.89).

V. The Appellant argued in the proceedings and at the oral hearing on 14 to 16 February 1989 substantially as follows:

(a) The requirements of Article 84 EPC should not be an issue in these proceedings since this was not a matter within Article 100 EPC. In any event, the requirements were met because the technology used is clear. The patent itself described only hybridisation procedures using conventional conditions. Test reports submitted on 19 January 1989 showed that under such conditions DNA sequences coding for IFN-α would not hybridize to IFN-β and . The definition of a polypeptide of the IFN-α type was given in the description which provided two tests for determining antiviral and immunological activities.

(b) The requirements of Article 83 EPC were met because it was enough that one way for carrying out the invention be described in detail and several ways were disclosed in the patent. The experimental results provided by

Respondent V (Innis' evidence) only showed that even a replacement of one amino acid can render the IFN-α inactive, although the corresponding DNA still hybridised. This clearly illustrates that the Respondents had not had any difficulty whatsoever to recognise that a DNA fell outside the claim. Thus no problem arose under Article 83 EPC, as long as there were specimen around which fell within the claim.

(c) The requirements of Article 54 EPC were met because "Lawn's gene bank", referred to in document (93) as a random collection of human genomic DNA fragments, corresponded to a library without a proper index. A person skilled in the art would not have considered screening Lawn's gene bank with IFN-α antibodies. He would even not have expected the DNA sequences of the bank to be directly expressible in E. coli. In addition to that, a short oligonucleotide sequence like one based on the Zoon's sequence would have promised false results. Because original Claim 6, corresponding to actual Claim 5, and other related claims were entitled to the priority of BIOGEN II, document (21a) "Streuli" could not be detrimental to the novelty of these claims.

(d) As far as the requirement for inventiveness according to Article 56 EPC were concerned, all plasmids and inserts specifically disclosed in document (16) "Nagata" encoded interferon IFN-α1. BIOGEN II disclosed for the first time expression vectors with unexpected higher activity on human cells or unexpected higher expression level than those disclosed in document (16).

(e) In any case, once the inventor had filed his first application for a subject-matter, he should be free to publish his invention. Without this principle being generally applicable the inventor would be obliged to maintain secrecy throughout the priority period. Matters published during such period, after filings, should be removed from the state of the art in order to satisfy the requirements of the Paris Convention.

VI. The Respondents submitted substantially the following arguments in the proceedings with regard to the issues involved in the decision of the first instance:

(a) The question of clarity and support was fundamental to sufficiency. Without proper limitations the skilled person would be at loss to know whether the products available to him would fall within the broad claims of the patent.

(b) Definitions of the kind used in Claims 1 to 3 were in essence testing programmes which should not be allowed to characterise materials claimed as such. The same claims were speculative in scope and contrary to the normal practice of the EPO.

(c) Claim 5, which was formerly Claim 6, represented subject-matter which was not novel. The priority date of this claim was only that of BIOGEN III, which meant that the "Streuli" (21a) publication fully anticipated its contents.

(d) As confirmed by the first instance, the "Nagata" (16) article provided the means to obtain the recombinant variants defined, in particular in Claim 2(d), in an obvious manner. The standard methods of approaching the

general problem of the patent were commonly known in the art and no inventive step was involved.

(e) It was further alleged that it was impossible, on the basis of the disclosure, to obtain the specific mature variant of IFN-α covered by Claim 17.

VII. The Respondents also formally requested and in writing that the following questions should be raised with the Enlarged Board of Appeal, namely (in the Board's own translation) whether or not

(i) Rule 28 EPC should be allowed to be used to circumvent the obligation for written disclosure with regard to a DNA sequence;

(ii) it is decisive that substantial ("materielle") priority should be supported

(a) either by a disclosure from which the subject-matter, for which priority is claimed, directly and unambiguously follows (in accordance with the Guidelines for Examination in the EPO, C-V, 2.3 and 2.4),

(b) or by a general disclosure (here by the disposition of a microorganism) from which the subject-matter, for which priority is claimed, has previously to be derived (here by means of experimentation involving many steps);

(iii) a claim is allowable which relates to a class of substances, if the class is characterised by a desired property, and otherwise only by the use of a

DNA for screening for a gene which codes for a member of such class.

VIII. The Appellant requested that the decision of the first instance be set aside and the patent be maintained on the basis of Claims 1 to 32, as submitted with the Statement of Grounds, Claims 28 and 29 being amended as submitted on 23 December 1988. As an auxiliary request Claims 1 to 29 were presented at the oral hearing, in which set Claims 5, 18 and 31 of the main set were deleted (formerly Claims 6, 20 and 33 of the decision under appeal).

The Respondents requested the Appeal to be dismissed.

At the conclusion of the oral hearing the Board's decision was announced in accordance with the Order set out below.

Reasons for the Decision

1. The appeal complies with Articles 106 to 108 and Rule 64 EPC and is, therefore, admissible.

2. **Amendments (Articles 123(2) and (3) EPC)**

2.1 Claims 1 to 3 of the main request are differently worded from that of the granted patent in as much as the phrase "exemplified but not limited to" has been deleted. There is no change in the remaining parts of Claims 1(a), 2(d) and 3(g) and the restriction in scope is necessary in particular when considering inventive step and priority. The request for amendment was therefore justified in the circumstances. The claims are now in line with the original disclosure and narrower in scope in consequence of the amendments.

2.2 Claims 28 and 29 are now restricted to a "sole" IFN-polypeptide instead of having "at least one polypeptide" (cf. former Claims 30 and 31). Since the earlier alternatives were expressly stated, the restriction is supported, clear and limiting the scope of the claim. The extension of the range of polypeptides to those in new Claims 16, 23, 24 and 25 is in consequence of a conversion of the former product-by-process claim 18 to a process claim (cf. below under 2.3). The same applies to Claim 29. This also justifies the corresponding amendment of the rest of these claims, which were formerly within the scope of original Claim 18, by including all possible polypeptides of choice. Thus, no extension of scope is involved.

2.3 Similar considerations apply to process Claim 16 based on former product Claim 18. The deletion of former Claims 14 and 17, and parts of Claims 15 and 16 (now Claims 14 and 15), as well as the slight changes of the wording of former Claims 19 and 21 (now 17 and 19) are also allowable.

No objections are therefore raised to the amendments presented in the claims under Articles 123(2) and (3) EPC.

3. Clarity and support (Article 84 EPC)

3.1 In this case, it was strongly urged by various Respondents that the patent was invalid and should be revoked on the basis that the claims defined the invention too broadly, because the description of the invention in terms of how to carry it out was much more limited in scope. The question therefore arises whether such an objection in opposition proceedings can be a proper basis for revocation of the patent (i) under article 100(b) which corresponds to Article 83 EPC, (ii) under Article 84 EPC.

3.2 As regards (i), Article 100(b) requires that the disclosure of a patent must be sufficiently clear and complete for the invention to be carried out by a person skilled in the art. This provision has previously been interpreted by the Board of Appeal in Decision T 292/85, "Polypeptide expressions", dated 27 January 1988 (to be reported in the O.J. EPO) as being satisfied "if at least one way is clearly indicated enabling the skilled person to carry out the invention". In other words, in the Board's view, it is not necessary for the purpose of Articles 83 and 100(b) EPC that the disclosure of a patent is adequate to enable the skilled man to carry out all conceivable ways of operating the invention which are embraced by the claims. As is discussed below, in the Board's view in the present case the disclosure is sufficient to enable the skilled man to carry out the invention claimed to the necessary extent. Thus the objections raised by the Respondents fail under Articles 83 and 100(b) EPC.

3.3 As regards (ii), Article 84 EPC reads:

"The claims shall define the matter for which protection is sought. They shall be clear and concise and be supported by the description".

This requirement is on its face quite distinct from the requirement of Article 83 EPC discussed above. Essentially, this requirement under Article 84 EPC is concerned with the permissible width of the claims having regard to the disclosure of the patent in its description. As discussed in Decision T 292/85 above, the scope of the protection sought in the claims must be fair having regard to the way in which the invention has been described, and having regard to the information which the skilled person has been given in the description as to how the invention can be carried out. The objections raised by the Respondents in

the present case are essentially objections to the effect that Article 84 EPC is violated by the claims of the patent in suit.

3.4 As has been stated in a number of previous decisions of the Boards of Appeal, Article 84 EPC is not a ground of opposition within Article 100 EPC, although the clarity of a claim and its scope may of course be a relevant factor when considering issues such as novelty and inventive step under Article 100(a) EPC. In the Board's view, objections to the scope of the claims, as raised in the present case, cannot in principle be an issue within Article 100(b) EPC in opposition proceedings.

3.5 In the present case, however, the Appellant has proposed various amendments to the text of the patent during these opposition proceedings. In this situation, Article 102(3) EPC is applicable, both in proceedings before the Opposition Division and in the appeal stage of opposition proceedings (having regard to Article 111(1) EPC). Article 102(3) EPC requires that, when amendments are made to a patent during opposition proceedings, the Opposition Division or the Board of Appeal shall consider, taking into consideration the amendments made, whether "the patent and the invention to which it relates meet the requirements of the Convention". This wording in Article 102(3) EPC is in marked contrast to the wording of Article 101(1) EPC (which is concerned with the scope of examination of an opposition to a patent, and which provides that such examination shall be as to "whether the grounds of opposition laid down in Article 100 prejudice the maintenance of the patent"), and with Article 102(1) and (2) EPC, which contain similar wording. In particular, "the requirements of the Convention" include Article 84 EPC, whereas "the grounds of opposition laid down in Article 100 EPC are listed in exclusive terms "(i.e. "only", "nur", and "ne ... que"),

without including Article 84 EPC or anything corresponding thereto.

3.6 The further question therefore arises in the present case, as to whether, on the proper interpretation of Article 102(3) EPC, the fact that any amendment to the patent has been made in opposition proceedings immediately and automatically throws open the possibility for an opponent to raise all objections which may arise under the EPC (including objections under Article 84 EPC); or whether, alternatively, the proper interpretation of Article 102(3) EPC requires, in effect, that when an amendment is made, before the patent is maintained in an amended form, it must then further be considered whether the amendments have themselves introduced any contravention of the requirements of the Convention.

3.7 In Decision T 227/88, "Detergent compositions" dated 15 December 1988 (to be reported in the O.J. EPO), the Board distinguished the powers under Article 102(1) and (2) EPC from these under Article 102(3) EPC as discussed above, and also stated in paragraph 3 of the Reasons: "When substantive amendments are made to a patent within the extent to which the patent is opposed, both instances have the power to deal with grounds and issues arising from those amendments even though not specifically raised by an opponent pursuant to Rule 55(c) EPC". It was not suggested that either instance had the power to deal with grounds or issues which did not arise from the amendments made and had not been raised by an opponent. Clearly the question whether an opponent could raise objections, under Article 84 EPC for example, which did not arise from the amendments made, was not in issue in that case.

3.8 In the Board's judgement, when amendments are made to a patent during an opposition, Article 102(3) EPC requires

consideration by either instance as to whether the amendments introduce any contravention of any requirement of the Convention, including Article 84 EPC; however Article 102(3) EPC does not allow objections to be based upon Article 84 EPC, if such objections do not arise out of the amendments made.

In support of this conclusion, it would seem to be somewhat absurd if the making of a minor amendment could enable objections outside Article 100 EPC to be raised which have no connection with the amendment itself.

4. Sufficiency (Article 83 EPC)

Repeatability

4.1 The reasoning in the decision under appeal that the alleged inadequacies in the definition of the recombinant plasmids in Claim 1(b) and (c), and consequent ambiguity in scope and the broad character of the claims, necessarily leads to a situation where the skilled person could not carry out the invention, cannot be followed. The special character of the invention must be taken into consideration.

4.2 The invention described in the patent in suit provides a route through recombinant DNA technology to certain types of interferons. The aim was to provide this kind of material in greater quantities at a reasonable price. This was achieved after considerable difficulties by a lengthy process but not in such a manner that would provide identical results each time when repeated.

4.3 As already mentioned, the Board has decided in earlier cases that the invention is sufficiently disclosed if at least one way is clearly indicated enabling the person

skilled in the art to carry out the invention (cf. T 292/85 above). In appropriate cases even specifically described examples need not be exactly repeatable. Variations in the starting materials are acceptable as long as "the claimed process reliably leads to the desired product" (cf. T 281/86, "Preprothaumatin", 27.1.88, to be reported in the O.J. EPO). In the case T 292/85 it was, for instance, held that the disclosure was sufficient in respect of the preparation of human hormones, where each person, as a source, could only provide an individual variant of the DNA precursor of the hormone, and there was of course no guarantee that such source would remain available to the public. The Board's reasoning in this respect was then based on circumstances where general methodology was involved and where not each and every starting material had to be made available in advance as long as the methods always worked.

4.4 The present case is somewhat different but nevertheless also relies on an open definition which relates to an unknown but probably finite number of human and animal interferons of the α-type. These materials would somewhat differ in constitution from each other but still represent some structural similarity in view of the affinity in hybridisation tests. Furthermore, as a class, the members provide end products with the same biological activity. As long as this is achieved by the invention there is no necessity to provide instructions in advance how each and every member of the class would have to be prepared. In view of the nature of the technique there is not even a guarantee that the same product is obtained from the same source after an identical repetition of the complicated and lengthy experiments. At this broad level, any one member of the class is an adequate representant of the invention.

4.5 It is therefore the view of the Board that variations in the construction within a class of genetic precursors, such as recombinant DNA molecules claimed by a combination of structural limitations and functional tests, are immaterial to the sufficiency of the disclosure provided the skilled person could reliably obtain some members of the class without necessarily knowing in advance which member would thereby be made available.

4.6 It is in the nature of processes starting from natural sources and aiming at genes coding for polypeptides that individual variations might inevitably occur. As long as the character of the use and, as in the present case, the type of activity of the end product is not changed such distinctions only represent inessential features. Whilst it would have been generally desirable to map all such structural variations in a general formula, this would have required a research programme of enormous magnitude, without immediate corresponding benefit. Such macromolecular precursors may in appropriate cases be defined as a class by the properties of the end products they relate to and by some structural characteristics, such as similarity based on capability of hybridisation with available structures, without necessarily creating uncertainty. In the present case the latter aspect is provided by hybridisation with nucleotide sequences made available in microorganisms which contain the basic structures, whilst the IFN-α type antiviral and immunological activity is limiting the class as a functional requirement.

4.7 Such considerations also apply to the Opposition Division's objection on the basis of the use of bacteria and other microorganisms in the testing and further expression, although only specific E. coli strains were available at

the priority date for the purpose. Claims relying on functionally defined features are already established in the genetic field (cf. Ibid, T 292/85) and the same should be applicable to a class which cannot otherwise be delimited with other terminology. This decision specifically discussed the broadening of such features to embrace means existing and to be discovered in the future. Unless claims with such functional connotations are allowable, no worthwhile protection is provided against a third party which faithfully repeats the process of the patent and obtains new but equally useful variants of the invention.

4.8 The above interpretation of the character of the invention as defined in Claim 1, has, of course, inevitable consequences for the requirements of sufficient disclosure under Article 83 EPC. There was no convincing evidence by the Respondents that the process relating to the claim, as described in the patent, is not reproducible in the sense that the skilled person would not obtain a useful precursor, which hybridises and leads to polypeptides of the IFN-α type, and which is therefore a member of the claimed class. The requirement that the skilled person should have instructions in the patent how to obtain any one claimed member in the class at will would be inappropriate and go too far in the field of genetic recombinants, and their broad classes.

4.9 There is, of course, the possibility that the skilled person might, on repeating the process of the patent, obtain some precursor candidates, among others, which might show borderline functional characteristics. The fact that in a set of candidates prepared in this manner a few are borderlines cases in as much as they show less marked functional characteristics than others becomes irrelevant

if indeed there are many others in the relevant core areas which are satisfactory. The problem for the skilled person may be real in some situations and this might be undesirable, but this does not affect the fact that members of the claimed class may be obtained with sufficient certainty and frequency.

The Board can therefore see the need for a partial reliance on functional characteristics in such situations, in view of the special circumstances which prevail in this field. Furthermore the Board does not agree that this point should be referred to the Enlarged Board of Appeal (cf. VII (iii)) because there is no question of lack of uniformity of the law in this respect, nor is there any important point of law in issue.

Deposition (Rule 28 EPC)

4.10 As regards depositions of precursors in living microbiological hosts, this could very well strengthen the disclosure supporting broad claims, for instance if a deposition establishes sources for structural standards for comparison, and starting points for modifications. It is a characteristic of the present case that the patentee has supported the description with a substantial number of deposited organisms which provide a great practical choice to outsiders exploring the invention further.

4.11 It was submitted that a deposition should never stand in lieu of a written disclosure whenever the structure can be determined by sequencing. However, in the present case, the deposition is not representing the claimed subject-matter, as such, as would be the case with novel and inventive microorganisms. Therefore, the request to refer the matter to the Enlarged Board of Appeal under Article 112 EPC

(cf. VII(i)) is not relevant to the issues in this case and must be rejected.

The reference to DNA molecules incorporated in deposited microorganisms could well be the definition of an available source, i.e. starting material, from which the desired plasmid or even part thereof may be obtainable. Thus, the deposition is an available starting point and can be interpreted as a basis of an implied product-by-process definition for the end-product in question since the latter can be reliably obtained by commonly known steps of isolation or be used in situ operatively for cloning etc.

The question of Claim 17

4.12 The alleged impossibility to obtain the specific mature variant of claim 17 was based on a statement by the inventor in a subsequent publication (cf. document (100), page 126). It appears from this that the "polypeptide produced by this and similar constructions was preceded by part of the signal sequence and by a few amino acids of ß-galactosidase, in no case was the signal sequence cleaved off correctly in E. coli". Such situations necessitate some additional steps on the basis of common general knowledge relating to the manipulation of polypeptide sequences, e.g. proceeding through a somewhat more elaborate construct, as suggested in the same article. In the absence of specific evidence showing that the particular compound cannot be obtained at all on such basis, this allegation is not accepted.

Conclusions on sufficiency

4.13 In view of the above, the Board finds no case for insufficiency. On the contrary, there is a detailed description of the actual reduction to practice of the

invention, and a great number of depositions which could provide a variety of immediate short cuts for the public to carry out the invention without having to go through the cumbersome route from natural sources. The description establishes a good basis for obtaining other variants, if this is desired. Nothing has been presented so far to cast doubt on the workability of the approach presented in the specification. The requirement for sufficiency is not a matter of satisfying the perfectionist but to enable the skilled person to handle the invention in normal practice.

5. Novelty (Article 54 EPC)

5.1 The decision of the first instance explained that some of the fragments contained in "Lawn's gene bank" were of the IFN-α type and therefore anticipated claim 1(b). According to Article 54(2) EPC the state of the art shall be held to comprise everything made available to the public before the date of filing of the European patent application.

If the conclusion drawn by the first instance from document (93) were correct, then the cloned library of large, random embryonic human DNA fragments, constructed by Lawn et al. as described in (93), would have made available to the public such DNA sequences which hybridise to any of the DNA inserts specifically named in paragraph (a) of Claim 1 and which code for a polypeptide of the IFN-α type.

5.2 However, the disclosure contents of citation (93) leave no doubt that DNA sequences according to Claim 1(b) had not been made available to the public by this publication itself or through this publication from the bank. When studying the document, the public, represented by a person skilled in the art, does neither get any indication at all

that "Lawn's gene bank" comprises any clone containing DNA sequences which code for a polypeptide of the IFN-α type (leukocyte interferon) nor does the public have a reasonable chance to trace out such DNA sequences within "Lawn's gene bank" by means of their hybridisation properties.

5.3 The skilled person would have recognised that the starting material for constructing "Lawn's gene bank" had been human fetal liver DNA, whereas the state of the art in the field of leukocyte interferon most preferably started from leukocytes which were induced by a specific treatment to produce acceptable levels of interferon activity. It was known that interferon messenger RNA is present in leukocytes at a very low level only. However, the skilled person would have also realised that (93) was exclusively concerned with the isolation and characterisation of specific globin genes for which purpose the cloned library of human DNA in question was screened by means of a specific cloned human ß-globin cDNA plasmid as a hybridization probe.

5.4 Provided that the skilled person were, by analogy, to consider screening "Lawn's gene bank" for any DNA sequences coding for a polypeptide of the IFN-α type, he would have been in need for an expedient hybridisation probe. But (93) clearly shows that only DNA sequences of considerable length, e.g. fragments from a specific ß-globin cDNA plasmid, containing the ß-globin gene portion, had been applied there as hybridisation probes.

Along these lines the skilled person to be able to uncover any DNA sequence according to Claim 1(b) among the DNA inserts hidden in the multitude of clones of "Lawn's gene bank" would have needed specific hybridisation probes of

comparable length which were not disclosed before the first priority date of the patent in suit.

5.5 Alternatively, any notional interrogation of the collection would have had to be carried out with oligonucleotide sequences, to be yet synthesised on the basis of members of the polypeptide chain identified by Zoon (108) as part of a lymphoblastoid interferon. It would have been necessary to synthesise corresponding nucleotide chains, taking degeneracy into consideration. Since the testing tools would have been shorter than, for instance, the patentee's "Hif-2h" sequence, and also still variable under the degeneracy rules, the field of interactions would have been much wider with much higher chance of hybridisation with candidates which were not to lead to active end products. Nor is there any direct and unambiguous implication involved which would have led the skilled person to any relevant fragments in the collection. Such exercise would have involved relying on other sources of information and publication, which is, of course, outside the scope for testing for novelty.

5.6 As a matter of general interest, it can be stated that even if some fragments of the collection were to have all the required properties, the availability of such material without undue burden has not been established. The fact that such phages are hidden in a random collection of 240 000 unidentified individual samples is not irrelevant to the issue.

Whilst there was undoubtedly reference in the patent to positive hybridisation results with the probe "Hif-2h", this does not yet imply that the independent criteria for IFN-α type activity after expression would have also been complied with as far as some materials in the gene bank

were concerned. No relevant tests in this respect were reported.

5.7 The assumed presence of some fragments satisfying the criteria of the claim is not like the incidental availability of an unindexed book in a library. The interrogation of a library material is, at least for some members of the public, a direct mental procedure. The collection in the present case must be interrogated by physical interactions, and a consequent biochemical process in each case. Although any vial containing the relevant phage is a separate entity here, it is impossible to get to the vial without working through ten thousands of samples. The circumstances are such as if the material were under lock and where the key has to be first manufactured and applied.

5.8 If anything, the situation resembles that prevailing with natural substances, since the availability of phages is not direct, and is rather like the isolation of a component or bacterium from soil where the same exists in admixture with other useless materials. Thus, the idea that the gene bank itself would once for all anticipate an invention relating to a nucleotide sequence which may be contained therein somewhere, cannot be sustained.

Accordingly, the mere existence of a DNA sequence coding for a polypeptide of the IFN-α type, within the multitude of clones of "Lawn's gene bank" cannot automatically mean that the chemical compound (polynucleotide) concerned does become part of the state of the art. The latter would only then be the case if the existence of the compound concerned had recognisably been made publicly available.

Claim 1(b), 2(e) and Claim 7 are novel.

6. **Priority (Articles 87 to 89 EPC) and novelty of Claim 5 (Article 54 EPC)**

6.1 Claim 5 of the main request was former Claim 6, and represents firstly an IFN coding sequence preceded by nucleotides which correspond to part of a signal sequence and secondly a sequence which elicits synthesis of IFN-α2, thus forming the operative part of the nucleotide sequence "HcIF-II-206". The same was published in document (21a), "Streuli", together with the relevant operative partial nucleotide sequence on 19 September 1980. The matter was only described in that detail in BIOGEN III, subsequently filed on 2 October 1980.

6.2 The Opposition division was correct in their decision that former Claim 6, and corresponding Claims 20 and 33 could only derive priority from Biogen III. The contention that the reference to the "II-206" sequence in Biogen II, and corresponding deposition of a strain containing the total sequence in a recombinant form establishes by implication priority for a part of the sequence, cannot be accepted. In its earlier decision T 81/87, "Preprorennin", dated 24 January 1989, (to be reported in the O.J. EPO), the Board emphasised that the subject-matter of the claims "must be clearly identifiable in the previous application as a whole", and must relate to the "same invention" when it comes to priority. The decision adds that the disclosure of all the essential elements must be express or "be directly and unambiguously implied by the text as filed". (cf. Points 5 and 13 of the reasons). Although the whole recombinant plasmid, and its incorporated "II-206" sequence was in toto disclosed in BIOGEN II, in consequence of the deposition and corresponding description of some characteristics of "II-206" the same does not apply to the

details, i.e. various component parts within these entities, which were not disclosed in BIOGEN II at all.

6.3 The above quoted decision also stated that "elements which are to be recognised as essential only later on, are not part of the disclosure".

It is the view of the Board that if an entity itself is disclosed to the skilled person, this does not necessarily mean that a component part is also disclosed for the purpose of priority if this cannot be envisaged directly and unambiguously as such, and requires considerable investigation to reveal its identity.

6.4 Thus the subject-matter of Claim 5, being based only on the operatively important part of the much longer "II-206" sequence was not established in BIOGEN II, but only by further disclosure in BIOGEN III. It is therefore anticipated by document (21a) expressly describing all these sequences. The same applies to new Claims 18 and 31.

6.5 The main request is therefore rejected but the auxiliary request on file, from which these claims have been excised, is not anticipated with regard to any claim and can be subject of further considerations. Hereinafter the references to claims will be numbered as shown in the auxiliary request.

6.6 In view of this conclusion in favour of the Respondents, the Respondents' request for referral to the Enlarged Board (cf. VII(ii)) is no longer justified under Article 112 EPC and is therefore refused.

7. Inventive step (Article 56 EPC)

Citability of "Nagata"

7.1 As appears from the summary of facts and submissions (see paragraph III(iv) above), the question of inventiveness was only considered by the Opposition Division in respect of Claims 2(d) and 12 which were held obvious in the light of the teaching of document (16). This document represents an article on synthesis in E. coli of a polypeptide with human leukocyte interferon activity published in Nature on 27 March 1980 under participation of, among others, Charles Weissmann, who is the inventor in the present case. The document has in the proceedings been generally referred to as Nagata after the name of one of the authors of the said article.

7.2 In the proceedings before the Opposition Division it was concluded that Claims 2(d) and 12 were entitled to the priority only of Biogen II filed on 3 April 1980, i.e. later than the publication of Nagata. The Proprietor of the patent (the Appellant) argued, however, that Nagata, by merely describing the subject-matter disclosed in Biogen I, which had been filed on 8 January 1980, i.e. before the publication of Nagata, could not form part of the state of the art vis-à-vis Claims 2(d) and 12 for the purpose of Article 56 EPC. In support of this argument, reference was made to Articles 87-89 EPC and, in particular, to Article 4B of the Paris Convention for the Protection of Industrial Property (hereinafter P.C.). This argument was not accepted by the Opposition Division, who considered Nagata citable against Claims 2(d) and 12 in view of the fact that it had been published before the priority date of these claims.

7.3 In his Statement of Grounds of Appeal the Appellant did not pursue the above argument but relied on the contention that the claims in question involved an inventive step over the teaching of Nagata. At a later stage of the proceedings before the Board, the Appellant however reverted to this legal issue and strongly defended the position taken in the opposition proceedings. The Respondents equally strongly contested that Nagata were to be excluded from the citable state of the art vis-à-vis Claims 2(d) and 12.

7.4 If this point of law alone had been decisive for the position of the Board, there might have been good reasons for referring the point to the Enlarged Board of Appeal. However, as will appear below, the Board takes the view that, irrespective of whether or not Nagata is citable, Claims 2(d) and 12 involve an inventive step over the teaching of Nagata. In this situation, the Board refrains from referring the point to the Enlarged Board of Appeal. Nevertheless, the Board considers it appropriate not to leave this matter, which is of general interest and considerable importance, entirely open but clarify its own position on this point of law.

7.5 The answer to the question whether or not Nagata is citable against Claims 2(d) and 12, depends upon the interpretation of the relevant provisions of the EPC on priority, i.e. Articles 87-89 EPC.

As explained by the Legal Board of Appeal in case J 15/80 (OJ EPO 1981, 213), these provisions are providing a self-contained priority system for the purpose of European patent applications since the P.C. is not formally binding upon the EPO. However, having regard in particular to the fact that the EPC constitutes a special agreement within the meaning of Article 19 of the P.C., the EPC is clearly intended not to contravene the basic principles of priority

laid down in the P.C. Consequently, the provisions of inter alia Article 4B P.C., explaining the fundamental effect of the right of priority, have also to be taken duly into account for the purpose of interpreting the relevant provisions of the EPC. In fact, the EPC, lacking a corresponding explicit explanation of the effect of the right of priority, has in this respect to be considered as being based on the same principles as laid down in Article 4B of P.C.

7.6 According to the provisions of Article 4B of the P.C. "any subsequent filing" during the priority year "shall not be invalidated" by, inter alia, the publication of the invention as covered by the first filing in the priority interval. This means, particularly, that such a publication will neither destroy the novelty of the invention, for which priority is claimed in the subsequent filing, nor diminish the inventive step embodied in it, as considered at the date of the first application on which the right to priority is based (cf. Bodenhausen's Guide to the application of the Paris Convention, BIRPI 1968, pages 40-43). This is, of course, aimed at enabling and even encouraging the inventor to make his invention known at an early stage, which is fully consistent with one of the basic objects of the patent system, namely to promote a rapid spread of information and technology. It also gives him a fair chance to make economic use of the invention within a reasonable period of time.

7.7 The above principles give rise to no major difficulties in straight-forward cases, where the subsequent filing covers exactly the same invention (subject-matters, elements etc.) as the first application from which priority is claimed. In the present case, however, the situation is more complicated in that the Appellant is claiming multiple

priorities for different claims of his European patent under consideration, which is allowed under Article 88 EPC provided, of course, that there is unity of invention within the meaning of Article 82 EPC (cf. Article 4F P.C.). In respect of Claims 2(d) and 12, he is claiming the priority of Biogen II, as stated above. These claims also contain subject-matters (specific DNA sequences) not covered by the disclosure of Biogen I, which is the first application from which priority is claimed. Thus, Biogen II represents a development of the invention as disclosed in Biogen I. Equally, Biogen III, which is the last application from which priority is claimed, represents a further development in relation to the disclosures in the two previous applications. In this respect it is to be noted that such extensions in later applications do not prevent protection from being recognised for those subject-matters of the invention which were already present in the previous applications (cf. Article 88(3) EPC and the guide referred to under paragraph 7.6, page 54) in multiple priority situations. In view of these considerations in the present case, the fact that BIOGEN II also contains subject-matter extending over the disclosure of BIOGEN I and that Claims 2(d) and 12 are only entitled to the priority of BIOGEN II does not prevent protection from being recognised from BIOGEN I for the subject-matter disclosed in that first application.

7.8 In the Board's view the legal situation can be summarised as follows.

When priority is claimed for a European patent application under Article 88 EPC, the publication (or any other disclosure within the meaning of Article 4B of the P.C. of the content of the priority application, in the interval between the filing of that application and the filing of the (final) European patent application cannot be used as

state of the art against any claim in the latter application. However, if such publication goes beyond the content of a previously filed application and includes subject-matters not covered by the disclosure of that application, such disclosure may in principle be cited against any claim in the (final) European patent application relying on a priority date subsequent to the publication date. It might be added that a different view on this matter would render the system of multiple priorities rather illusory.

7.9 The facts of the present case indicate clearly that Nagata is no more than effectively a true disclosure of the subject-matter of the Biogen I application relating to Claim 1 of the European patent under consideration. Thus the publication of Nagata after the filing of BIOGEN I does not affect the right to protection from BIOGEN I for the European patent application under consideration in respect of the subject-matter disclosed in Biogen I. In accordance with Article 89 EPC, this means that although Claims 2(d) and 14 are only entitled to the priority of BIOGEN II, nevertheless, the date of priority of BIOGEN I, i.e. 8 January 1980, shall count as the date of filing of the present European patent application in respect of the corresponding subject-matter. Consequently, Nagata would not form part of the state of the art vis-à-vis Claims 2(d) and 14 (or, in fact, any claim) of the European patent under consideration for the purpose of Article 56 EPC. There could, therefore, be no lack of inventive step with regard to these claims, as a matter of principle.

Inventive step in respect of "Nagata"

7.10 Even if the Nagata document were citable, the conclusion of the Opposition Division could not be maintained according to which the two plasmids of Claim 2(d) had not been

considered as involving an inventive step vis-à-vis the general teaching disclosed by Nagata of how to prepare plasmids capable of expressing in E. coli polypeptides having human leukocyte interferon activity.

7.11 As already stated Nagata discloses the relevant parts of BIOGEN I.

It describes inter alia, the relevant recombinants of Claim 1(a), i.e. containing the means for "fishing" for similar structures by the hybridisation reaction, such as the probe sequences "HcIF-4c", "HcIF-2h" and others. It was suggested that the publication of such results would enable the skilled person to obtain the relevant further specific sequences listed in Claim 2(d), as an obvious step.

7.12 The technical problem concerning such art would have been to obtain by further processing certain precursors with the given specific capabilities and particular structures. The solution of the problem was to provide specifically structures "II-206" and "SN35-AHL6" and not others. In fact the transformed hosts, (Claim 12) contain the inserts according to Claim 2(d) which show some surprising technical effects compared to the subject-matter disclosed by Nagata. Assuming a person of ordinary skill in the art had been successful in identifying a clone E. coli HB101(Z-pBR322(Pst)/HcIF-II-206) by recognising that the hybrid plasmid, abbreviated as "HcIF-II-206", of this clone, and its DNA insert, abbreviated as "Hif-II-206 fragment" are weakly hybridising to Hif-4c and Hif-2h fragment, both of which form subject-matter of Nagata, it could certainly not have been expected that the Hif-II-206 fragment is the precursor for an additional valuable interferon-like protein, called IFN-α2. When determining relative IFN activity (see EP-B-32 134, page 33, lines 10-29 and 35) by a procedure similar to that

disclosed in Nagata (see explanation to Table 3) IFN-α2 was about 30 times more active on human CCL23 cells than the structurally different IFN-α1 disclosed by Nagata.

These results indicate that the existing structural differences on the DNA and on the protein level, respectively, unexpectedly confer a valuable property to the subject-matter of Claims 2(d) and 12.

7.13 In this connection, Respondents have argued the higher antiviral activity, quoted in the patent (page 33, line 35) had been estimated only visually so that the assay in question had only roughly informing, qualitative character, which meant that such an inaccurate test could not satisfactorily demonstrate a patent-supporting effect. On the other hand, none of the Respondents have substantiated any results in support of the view that the biological activity, which in the above test on human cells was apparently in favour of IFN-α2, might be diminished or even reversed when applying a different more relevant assay for antiviral activity on human cells.

7.14 The modified plasmid, identified as Z-pBR322(Pst)/HcIF-SN35-AHL6 is also considered as possessing unexpected properties in comparison with the starting plasmid Hif-SN35, known from Nagata. Hosts transformed with this modified plasmid, (see Claim 12) produce about 100 times more of a protein displaying activity of human leukocyte interferon as compared to hosts, transformed with unmodified Z-pBR322(Pst)/HcIF-SN35 known from Nagata (compare Patent page 27, lines 53-63). This surprising technical effect in respect of yield is not obliterated by the observation that in E. coli a protein was produced having six additional amino acid residues fused to the amino terminal portion of the IFN-α1 (SN35) sequence. The Respondents submitted the view that the extension of the

protein sequence was, a priori, a distinct disadvantage without having substantiated this allegation. Lacking relevant experimental results there is no evidence in support of the view that the increase of protein expression by a factor of about 100 might finally turn into a disadvantage due to downstream processing or protein recovery.

Thus, the subject-matter of Claims 2(d) and 13 are based on an inventive step.

8. **Further matters**

In view of the above, the auxiliary request is allowable having regard to all grounds so far considered by the Opposition Division, including the objection of lack of inventive step with regard to Claims 2(d) and 12. The questions of inventive step in the case which have not so far been examined by the first instance should now be so examined.

Order

For these reasons, it is decided that:

1. All requests for the reference of points of law to the Enlarged Board of Appeal are rejected.

2. The main request is rejected.

3. The decision of the Opposition Division is set aside.

4. The case is remitted to the Opposition Division for further examination on the basis of the auxiliary request submitted during the oral proceedings.

The Registrar: The Chairman: