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**Datasheet for the decision
of 12 September 2017**

Case Number: T 1259/16 - 3.3.04
Application Number: 10194363.7
Publication Number: 2361924
IPC: C07K1/00, C07K1/14, C07K14/00,
C08G69/10
Language of the proceedings: EN

Title of invention:

Process for the preparation of mixtures of trifluoroacetyl
glatiramer acetate using purified hydrobromic acid

Patent Proprietor:

Teva Pharmaceutical Industries Ltd.

Opponents:

Generics [UK] Ltd (trading as Mylan)
Actavis Group ehf (opposition withdrawn)
Synthon BV
Hexal AG
G. L. Pharma GmbH (Intervener)

Headword:

Glatiramer acetate III/TEVA

Relevant legal provisions:

EPC Art. 105, 114(2), 123(2)

RPBA Art. 13(1)

Keyword:

Main request, auxiliary requests 1 to 32: amendments -
allowable (no)

Auxiliary requests 33 to 35: admitted (no)

Decisions cited:

G 0002/10, T 0686/99, T 0727/00, T 1241/03, T 0783/09,
T 2134/10, T 1649/10, T 1581/12, T 1536/14

Catchword:



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Case Number: T 1259/16 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 12 September 2017

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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
25 April 2016 concerning maintenance of European
patent No. 2361924 in amended form**

Composition of the Board:

Chairwoman G. Alt
Members: R. Morawetz
M.-B. Tardo-Dino

Summary of Facts and Submissions

- I. The appeals of the patent proprietor (hereinafter "appellant I") and of opponents 1, 3 and 4 (hereinafter "appellants II, III and IV" or "opponent-appellants") lie against the interlocutory decision of the opposition division concerning maintenance of European patent No. 2 361 924 in amended form.
- II. The patent in suit, entitled "*Process for the preparation of mixtures of trifluoroacetyl glatiramer acetate using purified hydrobromic acid*", was granted in respect of European patent application No. 10 194 363.7, published as EP 2 361 924 (hereinafter "application as filed"), which is a divisional application of European patent application No. 10 150 124.5 (hereinafter "parent application"), which in turn is a divisional application of European patent application No. 05 791 236.2, filed on 9 September 2005 and published as WO 2006/029393 (hereinafter "earlier application as filed").
- III. Four oppositions were filed, invoking *inter alia* the ground of Article 100(c) EPC that the subject-matter of the European patent extended beyond the content of the application as filed and the earlier application as filed.
- IV. The opposition division decided that the subject-matter of claims 20 to 28 and of claim 32 of the main request (claims as granted) did not meet the requirements of Articles 76(1) and 123(2) EPC. The subject-matter of claim 22 of auxiliary request 1d was considered not to meet the requirements of Articles 76(1) and 123(2) EPC. The patent was eventually maintained on the basis of the set of claims of auxiliary request 1f.

Claims 20 and 32 of the main request (claims as granted) read:

"20. A mixture of glatiramer acetate wherein the mixture has a desired molecular weight and less than 1000 ppm metal ion impurities.

32. Use of the mixture of trifluoroacetyl glatiramer acetate any one of claims 19 or 21-28 or the trifluoroacetyl glatiramer acetate of claim 30 in the manufacture of glatiramer acetate."

Claim 22 of auxiliary request 1d reads:

"22. Use of the mixture of trifluoroacetyl glatiramer acetate any one of claims 15 to 19 or the trifluoroacetyl glatiramer acetate of claim 20 in the manufacture of glatiramer acetate wherein the trifluoroacetyl glatiramer acetate is treated with piperidine."

Claims 2, 3 and 4 of auxiliary request 1f read:

"2. A process of producing a mixture of trifluoroacetyl glatiramer acetate, wherein the mixture has a desired average molecular weight comprising deprotecting a mixture of polypeptides each consisting of alanine, γ -benzyl glutamate, tyrosine and trifluoroacetyl lysine with a solution of hydrobromic acid in acetic acid, which solution is free of free bromine and comprises less than 100 ppm of metal ion impurities.

3. A process for obtaining a pharmaceutical composition containing a mixture of glatiramer acetate, and wherein the mixture has a desired average molecular weight, which comprises

- a) polymerizing N-carboxyanhydrides of tyrosine, alanine, γ -benzyl glutamate and N-trifluoroacetyl lysine to form a mixture of protected polypeptides;
- b) deprotecting the protected polypeptides with a solution of hydrobromic acid in acetic acid, which solution is free of free bromine and comprises less than 100 ppm of metal ion impurities, to form a mixture of trifluoroacetyl polypeptides;
- c) reacting the a mixture of trifluoroacetyl polypeptides with aqueous piperidine to form a solution of aqueous mixture of polypeptides, each of which consists of alanine, glutamic acid, tyrosine and lysine; and
- d) purifying the mixture of polypeptides.

4. A process of producing glatiramer acetate comprising the steps of:

- a) polymerizing N-carboxyanhydrides of tyrosine, alanine, γ -benzyl glutamate and N-trifluoroacetyl lysine to form protected glatiramer acetate;
- b) deprotecting protected glatiramer acetate with a solution of hydrobromic acid in acetic acid, the solution is free of free bromine and comprises less than 100 ppm of metal ion impurities, to form trifluoroacetyl glatiramer acetate;
- c) reacting trifluoroacetyl glatiramer acetate with aqueous piperidine to form a solution of glatiramer acetate; and
- d) purifying the glatiramer acetate."

V. Opponent 2 filed notice of appeal but no statement of grounds of appeal. By letter of 11 August 2016 it withdrew its opposition and ceased to be a party to these appeal proceedings.

- VI. With its statement of grounds of appeal appellant I maintained as its main request the claims as granted, auxiliary requests 1d, 1e and 1f, and also filed three new auxiliary requests, 1da, 1ea and 1fa.
- VII. Appellants II, III and IV in their statements of grounds of appeal raised objections *inter alia* as regards lack of a basis in the (earlier) application as filed for the combination of the features "*free of free bromine*" and "*less than 100 ppm of metal ion impurities*" present in claims 2 to 4 of auxiliary request 1f. In addition, appellants II and III requested acceleration of the appeal proceedings.
- VIII. The board decided to accelerate the appeal proceedings and issued a summons to oral proceedings.
- IX. In reply to the opponent-appellants' statements of grounds of appeal, appellant I filed auxiliary requests 1 to 32, in which auxiliary request 9 corresponded to former auxiliary request 1f.

Claim 16 of auxiliary request 1 read:

"16. A mixture of glatiramer acetate wherein the mixture has a desired molecular weight and less than 100 ppm metal ion impurities."

Claim 14 of auxiliary request 2 differed from claim 16 of auxiliary request 1 in that the feature "*100 ppm metal ion impurities*" had been changed to "*20 ppm metal ion impurities*".

X. Claim 16 of auxiliary request 3 read:

"16. Glatiramer acetate having a desired molecular weight and less than 100 ppm metal ion impurities."

Claim 14 of auxiliary request 4 differed from claim 16 of auxiliary request 3 in that the feature "*100 ppm metal ion impurities*" had been changed to "*20 ppm metal ion impurities*".

Claim 16 of auxiliary request 5 read:

"16. A mixture of glatiramer acetate wherein the mixture has an average molecular weight between 4,700 and 11,000 daltons and less than 100 ppm metal ion impurities."

Claim 14 of auxiliary request 6 differed from claim 16 of auxiliary request 5 in that the feature "*100 ppm metal ion impurities*" had been changed to "*20 ppm metal ion impurities*".

Claim 16 of auxiliary request 7 read:

"16. Glatiramer acetate having an average molecular weight between 4,700 and 11,000 daltons and less than 100 ppm metal ion impurities."

Claim 14 of auxiliary request 8 differed from claim 16 of auxiliary request 7 in that the feature "*100 ppm metal ion impurities*" had been changed to "*20 ppm metal ion impurities*".

Claims 2 to 4 of auxiliary requests 10, 13, 14, 17, 18, 21 and 22 and claim 1 of auxiliary requests 25, 26, 29 and 30 were directed to a process involving the use of

"a solution of hydrobromic acid in acetic acid, which solution is free of free bromine and comprises less than 100 ppm of metal ion impurities".

Claims 2 to 4 of auxiliary requests 11, 12, 15, 16, 19, 20, 23 and 24 and claim 1 of auxiliary requests 27, 28, 31 and 32 were directed to a process involving the use of *"a solution of hydrobromic acid in acetic acid, which solution is free of free bromine and comprises less than 20 ppm of metal ion impurities"*.

- XI. By letter of 3 May 2017 G.L. Pharma GmbH ("party as of right", hereinafter the "intervener") filed notice of intervention under Article 105 EPC.
- XII. In a communication pursuant to Article 15(1) RPBA the board gave its preliminary opinion in respect of some issues, *inter alia* with regard to auxiliary requests 1 to 8, which all included a claim corresponding to claim 20 as granted. It commented that it *"is not apparent that the described processes necessarily lead to GA having less than 100 (20 ppm) metal ion impurities"* (see points 13 to 15). It was inclined to agree with the opponent-appellants' submission that there was no basis in the application as filed for the combination of *"free of free bromine"* and *"less than 100(20) ppm metal ion impurities"* (see points 16 and 17). It was also inclined to agree with appellant II's submission that auxiliary requests 10 to 28 too contained at least one claim which included an unallowable combination of features which was not disclosed in the application as filed, i.e. a combination of a requirement for being free of free bromine and a threshold level of metal ion

contamination (variously 100 ppm or 20 ppm), and that this combination of features was also present in at least one claim of auxiliary requests 29 to 32 (see points 18 to 21).

XIII. In response, appellant I filed auxiliary requests 33 and 34 and announced the filing of an auxiliary request 35 as follows: "*[I]n the event that both AR33 and AR34 are considered inadmissible or unacceptable for any other reason, the patentee would (as AR35) delete claims 2-4 from whichever of AR9-24 the board considers to meet the requirements of Arts 76/123(2)EPC other than the combination point i.e. the resultant request would relate to a single independent process claim based on claim 1 of AR9.*"

Claim 1 of auxiliary request 33 read:

"1. A process of producing glatiramer acetate comprising the steps of:

- a) polymerizing N-carboxyanhydrides of tyrosine, alanine, γ -benzyl glutamate and N-trifluoroacetyl lysine to form protected glatiramer acetate;
- b) deprotecting protected glatiramer acetate with a solution of hydrobromic acid in acetic acid, the solution comprises less than 0.5% of free bromine and less than 100 ppm of metal ion impurities, to form trifluoroacetyl glatiramer acetate;
- c) reacting trifluoroacetyl glatiramer acetate with aqueous piperidine to form a solution of glatiramer acetate; and
- d) purifying the glatiramer acetate."

Claim 1 of auxiliary request 34 differed from claim 1 of auxiliary request 33 in that the feature "*0.5% of free bromine and 100 ppm of metal ion impurities*" had been changed to "*0.5% of free bromine and 20 ppm of metal ion impurities*".

- XIV. Oral proceedings were held on 12 September 2017. During the oral proceedings, appellant I filed auxiliary request 35, which was based on auxiliary request 9 with claims 2 to 4 deleted.

Thus, the single independent process claim 1 of auxiliary request 35 reads:

"1. In a process for obtaining a mixture of trifluoroacetyl glatiramer acetate, wherein the mixture has a desired average molecular weight and wherein during the process a batch of a mixture of polypeptides, each of which consists of alanine, γ -benzyl glutamate, tyrosine and trifluoroacetyl lysine is deprotected with a solution of hydrobromic acid in acetic acid, the improvement comprising use of a solution of hydrobromic acid in acetic acid, which solution comprises less than 100 ppm of metal ion impurities."

At the end of the oral proceedings the chairwoman announced the board's decision.

- XV. The following documents are referred to in this decision:

D4 WO2006/029393

D69 Expert report of Dr V. Bille (12 November 2015)

XVI. The arguments of appellant I may be summarised as follows:

Intervention by G.L. Pharma GmbH

No objection as regards the admissibility of the intervention was raised.

Main request

Admissibility

The main request was not a newly submitted claim request; it had always been part of the proceedings.

Article 100(c) EPC - claim 20

A basis for claim 20 could be found in the application as filed, as the claimed subject-matter was the direct product of several of the described processes, for example those found in paragraphs [0012], [0013] and [0064] in conjunction with paragraphs [0054] to [0060] of the application as filed.

The source of the discoloration of glatiramer acetate (GA) was traced to metal ion impurities in the hydrobromic acid in acetic acid (HBr/AcOH) solution that led to trifluoroacetyl glatiramer acetate (TFA-GA) and to GA/metal ion complexes, see paragraph [0092] of the application as filed.

By minimising the level of metal ion impurities in the HBr/AcOH solution, the level of said impurities in the TFA-GA and GA were reduced, thereby solving the problem of the coloured complexes.

It was clear that, just as the limitations regarding the metal ion content extended to the TFA-GA precursor, the same was logically applicable to the GA final product and that therefore the product of the processes would be GA of a desired molecular weight having less than 1000 ppm metal ion impurities.

Article 100(c) EPC - claim 32

Substantiation as to where a basis was found in the application as filed for the subject-matter of claim 32 could be derived from the arguments submitted in the statement of grounds of appeal for auxiliary request 1d.

Auxiliary requests 1 to 8

Article 123(2) EPC - claims corresponding to claim 20 of the main request

Auxiliary requests 1 to 8 all included a claim corresponding to claim 20 of the main request, and the basis in the application as filed for the subject-matter of these claims was that provided for said claim 20.

Auxiliary request 9

Article 123(2) EPC - claims 2 to 4

The application as filed related to two inventions - level of free bromine and level of free metal ions - both linked by being properties of the HBr solution used for deprotection. It included statements of the invention in paragraphs [0006] to [0013], which included limitations as to the level of free bromine and metal ion impurities, i.e. in combination, and thus

provided a clear pointer to the combination of preferred embodiments of the level of both free bromine and free metal ions which were set out in paragraphs [0020] to [0024] and paragraphs [0025] to [0031] of the application as filed, respectively. It was clear that the preferred levels of free bromine and metal ion impurities applied to each main embodiment and that the preferences applied in combination, i.e. both features could be varied independently and simultaneously.

Application of the reasoning given in decisions T 686/99 and T 727/00 was limited to situations where there was an absence of a clear pointer. In the present case, however, there was a clear pointer towards combining the embodiments of free bromine and metal ions, in that these two features were disclosed as narrowing cascades moving towards most preferred values. Thus, claims 2 to 4 did not create a combination that had not previously been contemplated.

Declaration D69 addressed impurities in active pharmaceutical products only at a general level, but not specifically in relation to controlling the levels of bromine and metal ions in the HBr solution.

The "*free of free bromine*" value was disclosed in example 4, which thus provided a pointer to it, and therefore combining it with a value from a list, i.e. "*less than 100 ppm metal ion impurities*", was allowable.

The present case was comparable to the cases underlying decisions such as T 1581/12 and T 2134/10, where a series of specified lengths of sequence fragments was

considered to be directly and unambiguously disclosed in conjunction with the disclosure of the full-length sequence, such as to permit their combination.

If the board were to see each percentage level of free bromine and each level of metal ions as a discrete feature, rather than as different degrees of the same feature, there was a disclosure of six percentage levels of free bromine and of seven metal ion limit levels, giving 42 possible combinations. Claim 2 of auxiliary request 9 covered five of these 42 combinations.

In similar circumstances, the competent board in decision T 783/09 (see Reasons, point 5.7) considered that claiming three out of 44 possible combinations did not contravene Article 123(2) EPC. In the present case, the skilled reader would clearly and unambiguously derive embodiments with no free bromine and less than 100 ppm metal ion from the application as filed, because all combinations of these two elements were disclosed.

In view of decision T 1241/03 (see Reasons, point 7) as well, the board should come to the conclusion that there was no added subject-matter.

Auxiliary requests 10 to 32

Article 123(2) EPC

It made no difference whether the metal ion content was specified as being 100 or 20 ppm, and it was not disputed that the "combination feature" was subject to the same objections as claims 2 to 4 of auxiliary request 9.

Auxiliary requests 33 and 34

Admissibility

In reply to the opponent-appellants' statements of grounds of appeal, a reasonable number of claim requests that addressed the issues raised in the appeal were submitted. With regard to added subject-matter, the objections raised by the opponent-appellants duplicated those raised in the case underlying decision T 1536/14 (parent case). Therefore, requests to take account of the added subject-matter objections that had been discussed in that case were submitted. The claim requests at the time in the case underlying decision T 1536/14 included combinations of free bromine and metal ion impurities, and the "combination" argument had not been of concern to the board then.

Auxiliary requests 33 and 34 were submitted to take account of the present board's preliminary opinion in its communication under Article 15(1) RPBA. They were identical to auxiliary requests 25 and 27, respectively, but the previous amendment reducing the level of free bromine had been removed, so that this feature reverted back to "*0.5% of free bromine*", as in the granted claims. The only amendment compared to the original language on pages 6 and 7 of the application as filed was therefore limited to the reduction in the level of metal ion impurities to 100 ppm.

These amendments did not raise any new issues.

For reasons of procedural economy the requests should therefore be admitted, even if they had been filed at a late stage.

Auxiliary request 35

Admissibility

The filing of this request had been announced in advance in writing. It was therefore clear that the intention had been to file a claim request with a single independent process claim based on claim 1 of auxiliary request 9.

As the board in its communication had not taken up any of the other added subject-matter objections raised by the opponent-appellants, such a request was clearly admissible.

- XVII. The arguments of appellants II, III and IV and of the intervener may be summarised as follows:

Intervention by G.L. Pharma GmbH

G.L. Pharma GmbH was entitled to join the appeal proceedings because the patent proprietor had initiated injunction proceedings against it.

Main request

Admissibility

Appellant I had failed to provide any reasoned arguments as to why the opposition division was wrong to find that the subject-matter of claims 27, 28 and 32 did not comply with the requirements of Articles 76(1) and 123(2) EPC. The main request should thus be

excluded from the proceedings (Article 12(4) RPBA) or be held inadmissible (Article 12(2) RPBA), see also decision T 1649/10 and the Case Law of the Boards of Appeal, 8th edition 2016, section IV.E.4.2.4.

Article 100(c) EPC - claim 20

The application as filed referred to trifluoroacetyl (TFA) polypeptides containing less than 1000 ppm metal ion impurities, and to processes comprising the use of a solution of HBr/AcOH containing less than 1000 ppm metal ion impurities. However, in the application as filed it was not disclosed that the use of these TFA polypeptides and an HBr/AcOH solution, respectively, necessarily led to a GA having a metal ion impurities content of less than 1000 ppm.

There was no direct and unambiguous connection between the amount of metal ion impurities in the HBr/AcOH solution and the amount of metal ion impurities in the GA product.

While in certain circumstances modifying the level of impurities in the earlier stages of the production of GA could have an effect on the impurities in the final GA, this was not necessarily the case. The claims used open wording, such that further sources of impurities were not excluded.

Appellant I's submission also did not take into account the metal ion content of any other component used for the production of TFA-GA and GA, such as starting materials and solvents.

Article 100(c) EPC - claim 32

The opposition division's assessment was correct. No arguments had been submitted by appellant I to support why the board should overturn the opposition division's decision.

Auxiliary requests 1 to 8

Article 123(2) EPC - claims corresponding to claim 20 of the main request

These auxiliary requests all failed to meet the requirements of Article 123(2) EPC for reasons analogous to those presented in respect of the main request.

Auxiliary request 9

Article 123(2) EPC - claims 2, 3 and 4

The features "*free of free bromine*" and "*less than 100 ppm of metal ion impurities*" related to separate inventive concepts and were described in separate embodiments within the application as filed.

The metal ion impurities limit of 100 ppm metal ions was selected from a list of at least seven individual embodiments ranging from "*free of metal ion impurities*" to "*less than 1000 ppm of metal ion impurities*".

Likewise with regard to the "*free of free bromine*" feature, the application disclosed a list of several embodiments ranging from "*less than 0.1% of free bromine*" to "*free of free bromine*".

There was no basis for a combination of the "*less than 100 ppm of metal ion impurities*" feature with the "*free of free bromine*" feature.

The application did not distinguish between preferred and less preferred embodiments, and all embodiments were disclosed as equally suitable.

The application did not contain any pointer towards combining a particular free bromine content and a particular metal ion impurities limit, except for a free bromine content of less than 0.5% and a metal ion impurities level of less than 1000 ppm.

Contrary to the opposition division's opinion, the "*free of free bromine*" feature was not singled out as the most preferred embodiment in the application as originally filed. It was selected from a list of equally suitable alternatives.

An HBr solution which was free of free bromine was difficult to obtain, and so it might not be the most preferred embodiment at all. Declaration D69 addressed the relevant understanding of the skilled person, see points 9 and 10. The skilled person reading the application as filed with that knowledge would not necessarily understand the narrowing cascades as moving towards most preferred values.

Example 4 provided no basis for the combination of the features "*free of free bromine*" and "*free of metal ion impurities of less than 100 ppm*" because it disclosed an HBr solution free of both bromine and metallic impurities. These limits were disclosed in combination in the example and could not be separated.

In decisions T 1581/12 and T 2134/10 the circumstances were such that the features were not selected from independent lists.

In decision T 783/09 the reference to particularly preferred combinations of features was explicitly disclosed in the application as filed.

Decision T 1241/03 related to a different situation, as there the application contained no lists of different concentrations.

Auxiliary requests 10 to 32

Article 123(2) EPC

These auxiliary requests all contained at least one claim which had a combination of a requirement for being free of free bromine and a threshold level of metal ion contamination, variously 100 ppm or 20 ppm. Neither combination had a basis in the application as filed.

Auxiliary requests 33 and 34

Admissibility

These requests should not be admitted into the appeal proceedings.

The objections against the combination of metal ion concentrations and free bromine content had been on file for the entirety of the appeal proceedings. It was well-established that where a preliminary opinion of the board only addressed submissions made by the parties and did not introduce any new issues, it could

not be used to justify the admission of new claim requests.

The combination of free bromine level and metal ion impurities as claimed now had not been claimed in any of the granted claims, nor had it been part of any claim request before. The only request which contained the 0.5% free bromine feature was the main request, which however had not been defended by appellant I. Thus, the combination of features was completely new.

Auxiliary request 35

Admissibility

The board should exercise its discretion not to admit this request into the appeal proceedings.

The present request had been submitted only during the oral proceedings.

Beforehand, the filing of 16 potential auxiliary requests had been foreshadowed, but none had actually been submitted.

The filing was not in reaction to unexpected or unforeseeable developments.

XVIII. Requests

Appellant I (patent proprietor) requested that the decision under appeal be set aside and that the patent be maintained as granted or on the basis of one of auxiliary requests 1 to 8 as filed with the reply to the opponent-appellants' statements of grounds of

appeal. It further requested that the opponent-appellants' appeals be rejected (auxiliary request 9) and, as further auxiliary requests, that the patent be maintained on the basis of one of auxiliary requests 10 to 32 filed with the reply to the opponent-appellants' statements of grounds of appeal, or on the basis of auxiliary requests 33 or 34 as filed with the letter of 10 August 2017, or on the basis of auxiliary request 35, filed during the oral proceedings before the board.

Appellants II, III and IV (opponents 1, 3 and 4) and the party as of right (intervener) requested that the decision under appeal be set aside and that European patent No. 2 361 924 be revoked.

Reasons for the Decision

Admissibility of the appeals and the intervention; parties to the proceedings

1. The appeals of appellant I (patent proprietor) and of appellants II, III and IV (opponents 1, 3 and 4) are admissible. Furthermore, the intervention complies with the requirements of Article 105 EPC and is therefore admissible. Consequently, the intervener is a party to the appeal proceedings as of right.

Main request (set of claims as granted)

Admissibility

2. Appellant II requested that the main request be excluded from the appeal proceedings by virtue of Article 12(4) RPBA, and appellant III and the party as

of right (hereinafter "intervener") requested that the main request be held inadmissible by virtue of Article 12(2) RPBA for lack of substantiation in the statement of grounds of appeal for the subject-matter of claims 27, 28 and 32.

3. With regard to appellant II's request, Article 12(4) RPBA stipulates that a board has the power to hold inadmissible requests which could have been presented or were not admitted in the first-instance proceedings.

The present main request had been dealt with in the first-instance proceedings, and it underlies the decision under appeal (see reasons, points 24 to 24.2.5). The request was maintained by appellant I in its statement of grounds of appeal (see pages 1 to 3) and thus forms part of appellant I's appeal (Article 12(1) RPBA). Accordingly, the board has no power to exclude this request from the appeal proceedings pursuant to Article 12(4) RPBA.

4. As to the request of appellant III and the intervener, the board observes that there are decisions, cited in the Case Law of the Boards of Appeal, 8th edition 2016, section IV.E. 4.2.4 under the heading "*Unsubstantiated requests*", in which auxiliary requests - filed during appeal proceedings without any substantiation and mostly at later stages of the proceedings - were held inadmissible by the boards. However, the circumstances underlying these decisions were different from the present circumstances, i.e. the admissibility of a

claim request dealt with in a decision under appeal and where substantiation is lacking for only some of the claims. Accordingly, the board decided to reject the request to hold the main request inadmissible.

Article 100(c) EPC - claim 32

5. The opposition division held that the subject-matter of claim 32 of the main request failed to meet the requirements of Articles 76(1) and 123(2) EPC (see decision under appeal, points 24.2.2 to 24.2.5). It considered that the (earlier) application as filed disclosed glatiramer acetate (GA) manufacturing processes which comprised the step of reacting trifluoroacetyl glatiramer acetate (TFA-GA) with aqueous piperidine. This step was not a feature of the subject-matter of claim 32, and the (earlier) application as filed did not disclose the general use of TFA-GA to manufacture GA in the absence of the reacting of TFA-GA with aqueous piperidine, and therefore this claim did not meet the requirements of Articles 76(1) and 123(2) EPC.
6. Appellant I's statement of grounds of appeal does not specifically address the issue of the basis for the subject-matter of claim 32 in the (earlier) application as filed. However, appellant I submitted that the reasoning provided in the statement of grounds of appeal with regard to the basis for the subject-matter of claim 22 of auxiliary request 1d also explained where the basis was to be found for the subject-matter of claim 32 of the main request.
7. Claim 22 of auxiliary request 1d relates to the use of TFA-GA in the manufacture of GA and comprises the step "*wherein the trifluoroacetyl glatiramer acetate is*

treated with piperidine" (see section IV). The reasoning provided in the statement of grounds of appeal addresses the issue of why the subject-matter of claim 22 does not need to specify that the piperidine used in the conversion of TFA-GA to GA is "*aqueous piperidine*". Therefore, this argument does not address the objection raised by the opposition division against the subject-matter of claim 32 (see point 5).

8. Thus, the board finds that the reasons given for setting aside the decision under appeal as regards the finding of the opposition division of lack of a basis in the (earlier) application as filed for the subject-matter of claim 32 are not persuasive.
9. Consequently, the board decides that the ground for opposition under Article 100(c) EPC prejudices the maintenance of the patent as granted because at least claim 32 relates to subject-matter extending beyond the content of the (earlier) application as filed (Articles 76(1) and 123(2) EPC).

Auxiliary requests 1 to 8

Article 123(2) EPC - claims corresponding to claim 20 of the main request

10. The opposition division held that minimum levels of ppm metal ion impurities had been disclosed in association with the HBr solution or the trifluoroacetyl polypeptide mixture, but not as features of the GA end product as such, and that therefore the subject-matter of claim 20 of the main request did not meet the requirements of Articles 76(1) and 123(2) EPC (see decision under appeal, point 24.2.3).

11. Auxiliary requests 1 to 8 all include a claim corresponding to claim 20 of the main request directed to (a mixture of) glatiramer acetate (GA) having a desired molecular weight (an average molecular weight between 4,700 and 11,000 dalton) and less than 100 ppm (20 ppm) metal ion impurities (see section IX).
12. Appellant I submitted that the basis for these claims was the same as that submitted for claim 20 of the main request.
13. It has been established (cf. decision G 2/10, OJ EPO 2012, 376) that the "*gold standard*" for assessing compliance with Article 123(2) EPC is that any amendment to the parts of a European patent application or of a European patent relating to the disclosure (the description, claims and drawings) can only be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of these documents as filed.
14. It was undisputed that GA containing less than 1000 (or 100 or 20) ppm metal ion impurities was not disclosed explicitly in the application as filed. However, appellant I submitted that the claimed GA was the direct product of several of the processes described in the application as filed and that it would be clear to the skilled person that the controlled levels of metal ion impurities applied not only to the TFA-GA precursor material but also to the GA product.
15. The board is not persuaded by this line of argument. The application as filed discloses processes comprising the use of a solution of hydrobromic acid in acetic

acid (HBr/AcOH) containing less than 1000 ppm of metal ion impurities (see paragraphs [0012], [0013] and [0064]). The application also discloses mixtures of trifluoroacetyl polypeptides comprising variable amounts of metal ion impurities, e.g. less than 1000 ppm, less than 100 ppm and less than 20 ppm (see paragraphs [0054] to [0060]).

16. However, in the application as filed it is not disclosed that the use of this HBr/AcOH solution and trifluoroacetyl polypeptides, respectively, necessarily leads to GA having a metal ion impurities content of less than 1000 ppm.

17. Moreover, there also appears to be no direct and unambiguous connection between the amount of metal ion impurities in the HBr/AcOH solution and the amount of metal ion impurities in the GA product, since on the one hand the processes are disclosed using open language such as "*comprising the steps*" and on the other hand the metal ion content of any possible other component used in the process for the production of GA is not specified in the application as filed (see paragraphs [0012], [0013] and [0064]).

For the same reasons there is also no direct and unambiguous connection between the amount of metal ion impurities in the TFA-GA precursor material and in the GA product.

18. In the board's judgement, the skilled person would therefore not derive directly and unambiguously from the application as filed, using common general knowledge, that the disclosed processes necessarily lead to GA having less than 1000 ppm metal ion impurities.
19. According to auxiliary requests 1 to 4, the level of metal ion impurities in GA is reduced to 100 ppm, and in auxiliary requests 5 to 8 it is further reduced to 20 ppm (see section IX). However, for the same reasons as set out above for the subject-matter of claim 20 of the main request (see points 13 to 18), it is not apparent that the processes disclosed in the application as filed necessarily lead to GA having an even lower content of metal ion impurities.
20. The board concludes from the above that the subject-matter of the claims of auxiliary requests 1 to 8 corresponding to claim 20 of the main request does not meet the requirements of Article 123(2) EPC. Therefore auxiliary requests 1 to 8 are not allowable.

Auxiliary request 9 - request corresponding to auxiliary request 1f maintained by the opposition division

Articles 123(2) EPC - claims 2, 3 and 4

21. The subject-matter of claims 2, 3 and 4 of auxiliary request 9 is directed to methods which comprise the use of "*a solution of hydrobromic acid in acetic acid, which solution is free of free bromine and comprises less than 100 ppm of metal ion impurities*".
22. The opposition division held that the application as filed provided a basis for the claimed subject-matter

(see decision under appeal, point 27.2). The opponent-appellants and the intervener disagreed with this finding in the decision under appeal.

23. It was undisputed between the parties that the claimed combination of the features characterising the solution of hydrobromic acid in acetic acid - "*free of free bromine*" and "*less than 100 ppm of metal ion impurities*" - is not explicitly disclosed in the application as filed.
24. At issue is thus whether or not the claimed combination of features can be derived directly and unambiguously, using common general knowledge, from what is explicitly disclosed in the application as filed, i.e. whether the combination is implicitly disclosed.
25. It is established case law that the content of an application must not be considered to be a reservoir from which individual features pertaining to separate embodiments of the application can be combined in order to create a particular combination. In the absence of any pointer to that particular combination, this combined selection of features does not, for the person skilled in the art, emerge directly and unambiguously from the content of the application as filed. The fact that features in question have been mentioned in the description as "*preferred*" may act as a pointer (see Case Law of the Boards of Appeal, 8th edition 2016, section II.E.1.4.1 and the decisions cited there).
26. Appellant I submitted (i) that the preferred levels of free bromine and metal ion impurities were individualised preferences that were clearly understood as being applicable in combination, (ii) that the application as filed disclosed the levels of free

bromine and metal ion impurities as narrowing cascades moving towards most preferred values, (iii) that example 4 provided a basis for the claimed combination and (iv) that case law such as in decisions T 1581/12, T 2134/10, T 1241/03 and T 783/09 supported its case (see section XV).

27. The board will address appellant I's various lines of argument in turn.
28. As regards appellant I's first line of argument, the application as filed discloses "*a solution of hydrobromic acid in acetic acid, which solution comprises less than 0.5% of free bromine and less than 1000 ppm of metal ion impurities*" (see paragraphs [0009] and [0019] and similarly in paragraphs [0012] and [0013]) and thus a specific combination of levels of free bromine and metal ion impurities which differs from the claimed combination.
29. The levels of free bromine in the solution of hydrobromic acid in acetic acid (HBr/acetic acid) are set out individually in paragraphs [0020] to [0024] of the application as filed and range from "*less than 0.1% of free bromine*" to "*free of free bromine*".
30. In a separate list, the levels of metal ion impurities in the solution of HBr/acetic acid are set out individually in paragraphs [0025] to [0031] of the application as filed and range from "*less than 1000 ppm of metal ion impurities*" to "*free of metal ion impurities*".
31. None of these embodiments in paragraphs [0020] to [0031] of the application as filed is characterised explicitly as being preferred. Rather, these

embodiments are characterised variously as "*in one embodiment*", "*in another embodiment*", "*in a further embodiment*" and "*in yet another embodiment*". Thus, in the board's judgement, all the various levels of free bromine and metal ion impurities have to be considered to represent equally suitable alternatives.

32. Furthermore, while the levels of free bromine and metal ion impurities are both features of the HBr/acetic acid solution, each of them in fact solves a different problem. Thus, free bromine leads to bromination of tyrosine residues in TFA-GA (see paragraph [0086] of the application as filed), while metal ion impurities in HBr are chelated by TFA-GA and GA and the resulting metal complexes contribute to coloration of the GA solution (see paragraphs [0090] to [0093] of the application as filed). Accordingly, in the board's view, the skilled person reading the application as filed as a whole has no reason to understand that the levels of free bromine and metal ion impurities of the HBr/acetic acid solution are connected and to be varied in combination. Therefore, the disclosure of one specific solution comprising a particular combination of levels of free bromine and metal ion impurities (see point 28) provides no pointer to all possible other such combinations.
33. In summary, appellant I's first line of argument thus fails since the claimed levels of free bromine and metal ion impurities are not disclosed as preferred embodiments, nor does the application as filed provide a pointer to the combination of any level of free bromine and metal ion impurities beyond the explicitly disclosed combinations (see point 28 above and point 36 below).

34. Appellant I's second line of argument hinges on the submission that the application as filed discloses the levels of free bromine and metal ion impurities as narrowing cascades moving towards most preferred values.
35. However, in the board's view, the skilled person reading the application as filed would not recognise from the mere depiction of the levels of free bromine and metal ion impurities as narrowing cascades that the lower values are necessarily more preferred or that the lowest level is the most preferred. This is because the skilled person is aware that, while the product produced, i.e. GA, has to be safe, reducing the levels of impurities can be time-consuming, difficult and expensive, and reducing impurities to as low a level as possible is both impractical and uneconomical (see declaration D69, point 10). Therefore, while the skilled person would want to control the level of impurities, this does not mean that, all things being considered, the lowest level of impurity is necessarily the most preferred. Hence, appellant I's second line of argument also fails.
36. As regards appellant I's third line of argument, Example 4 relates to the colour determination of HBr/ acetic acid solutions and discloses that "*the color of these batches of HBr/acetic acid indicated that they were essentially free of bromine and metal ion impurities*" (see paragraph [0115] of the application as filed). Thus, in terms of levels of impurities Example 4 discloses that the solution is "*essentially free*" of both free bromine and metal impurities. However, the disclosure of this combination in Example 4, i.e. the reduction of both types of impurity to the lowest level, does not provide a pointer to the claimed

combination in which "*free of free bromine*" is combined - not with "*essentially free of metal ion impurities*" - but with "*less than 100 ppm of metal ion impurities*". Therefore, the board is also not persuaded by appellant I's third line of argument.

37. As regards appellant I's reliance on the case law, the board considers that the factual basis of decision T 1581/12 of 15 September 2016 (see Reasons, point 7) and of decision T 2134/10 of 14 November 2013 (see Reasons, point 11) is not comparable to the factual basis of the present case. In the cited decisions, the combination of features was allowed because it was considered to be derived from two lists which were not independent of each other. In the present case, however, the lists relating to free bromine levels and metal ion impurities are fully independent (see also points 29, 30 and 32), and appellant I itself submits that the limits relating to free bromine and metal ion impurities can be varied independently (see section XV). As acknowledged in decision T 1581/12 with reference to established case law, in such a situation, in the absence of a clear pointer, the association of one member of one list with another member of the other list results in a combination which is considered to create new subject-matter (see Reasons, point 7).
38. In decision T 783/09 of 25 January 2011 (see Reasons, points 5.7 to 6.2) the reference to particularly preferred combinations of features was explicitly disclosed in the application as filed, and no particular quality was attributed to any of the very preferred combinations, resulting in a list of forty-four qualitatively equal elements, of which forty-one

could be deleted. As pointed out above (see point 31), in the present case none of the impurity levels is characterised as being preferred, let alone as being very preferred.

39. Decision T 1241/03 of 1 September 2005 (see Reasons, points 6 and 7) also relates to a different situation, as there the application contained no lists of equally suitable parameters, and the preferred value for each parameter was indicated explicitly in the application as filed. In the light of this disclosure the board considered that the combination of compounds in specific concentrations found a basis in the application as filed.
40. As the present case is not comparable to cases such as those underlying decisions T 2134/10, T 1581/12, T 1241/03 and T 783/09, appellant I's reliance on that case law does not help its case either.
41. The board concludes from the above that the claimed combination of features results from a selection from two fully independent lists. Since the application as filed does not provide a pointer to the claimed combination, the subject-matter of claims 2 to 4 of auxiliary request 9 does not meet the requirements of Article 123(2) EPC. Hence, auxiliary request 9 is not allowable.

Auxiliary requests 10 to 32

Article 123(2) EPC

42. Auxiliary requests 10 to 32 all contain at least one independent claim which includes a combination of a requirement that the solution of hydrobromic acid in

acetic acid be free of free bromine and a threshold level of metal ion contamination (variously 100 ppm or 20 ppm), see section IX.

43. In the context of auxiliary request 9 the combination of the features "*free of free bromine*" and "*less than 100 ppm of metal ion impurities*" had been considered by the board (see points 21 to 41). In the board's opinion this analysis is equally applicable to the combination of the features "*free of free bromine*" and "*less than 20 ppm of metal ion impurities*". This was not disputed by appellant I.
44. Accordingly, the board decides that the subject-matter of claims 2 to 4 of auxiliary requests 10 to 24 and the subject-matter of claim 1 of auxiliary requests 25 to 32 do not meet the requirements of Article 123(2) EPC. These requests are therefore not allowable.

Auxiliary requests 33 and 34

Admissibility

45. In auxiliary request 33 the solution of hydrobromic acid in acetic acid is now characterised as comprising "*less than 0.5% of free bromine and 100 ppm of metal ion impurities*", while according to auxiliary request 34 it comprises "*less than 0.5% of free bromine and 20 ppm of metal ion impurities*".
46. Auxiliary requests 33 and 34 were filed in reaction to the communication issued by the board pursuant to Article 15(1) RPBA setting out its preliminary opinion on some of the issues in the appeal proceedings.

Moreover, the combinations of features now claimed had not been claimed before and thus represented an amendment to appellant I's case.

Consequently, under Article 114(2) EPC and Article 13(1) RPBA, the admission of these requests is at the board's discretion.

47. Appellant I submitted that auxiliary requests 33 and 34 had been submitted to take account of the board's preliminary opinion in the communication pursuant to Article 15(1) RPBA with regard to an objection under Article 123(2) EPC.
48. The board observes that the objection at issue here, which the amendments made in auxiliary requests 33 and 34 aimed to address, was not a new one. It had been raised by all opponent-appellants in their respective statements of grounds of appeal (see section VII) and was thus known to appellant I. In fact, the only new piece of information for appellant I was the board's indication that it was inclined to agree with the opponent-appellants' objection.
49. The board therefore considered that in these circumstances the board's communication and the preliminary opinion given therein cannot be taken as justification for the admissibility of new requests submitted only in reply to said opinion in the communication (see also Case Law of the Boards of Appeal, 8th edition 2016, section IV.E.4.4.12).
50. The board further considered that the suggested amendments would have added considerably to the complexity of the case, as the claimed combination of features had not been present in any of the granted

claims or in any of the higher-ranking pending claim requests, but stemmed from the description and thus had not been considered before.

51. Moreover, the combination of features was unexpected. In fact, appellant I had not pursued the "*less than 0.5% free bromine*" feature before the opposition division, and the only claim request in the appeal proceedings containing this feature - albeit in combination with the feature "*less than 1000 ppm metal ion impurities*" - was the main request, while all 32 auxiliary requests filed in response to the opponent-appellants' statements of grounds of appeal contained the "*free of free bromine*" feature. The proposed amendments thus went beyond what had to be considered to be the framework of these appeal proceedings.
52. Finally, the board considered that no substantiation as to the novelty and inventive step of the claimed subject-matter was submitted when filing auxiliary requests 33 and 34, and so it was not immediately apparent to the board that these claim requests - in case they were found to fulfil the requirements of Article 123(2) EPC - could be dealt with without adjournment of the oral proceedings or remittal of the case. In the board's view, admitting these claim requests would thus not have served procedural economy.
53. Hence, the board decided to exercise its discretion not to admit auxiliary requests 33 and 34 into the proceedings in accordance with Article 114(2) EPC and Article 13(1) RPBA.

Auxiliary request 35

Admissibility

54. This claim request is based on auxiliary request 9 with deletion of those claims that were considered by the board not to meet the requirements of Article 123(2) EPC.

It was filed during the oral proceedings after the board had given its opinion on auxiliary requests 1 to 32 and had further decided not to admit auxiliary requests 33 and 34 into the appeal proceedings.

Thus, the filing of this request likewise constituted an amendment to appellant I's case, and its admission was at the board's discretion (Article 114(2) EPC and Article 13(1) RPBA).

55. The appellant submitted (i) that the filing of this request had been announced in advance in writing and (ii) that the request was clearly admissible, as the board in its communication pursuant to Article 15(1) RPBA had not taken up any of the other added subject-matter objections raised by the opponent-appellants, and those which had been dealt with no longer applied.

56. As to the first argument, even though the filing of auxiliary request 35 had been announced in writing - albeit only as one of 16 possible auxiliary requests (see section XII) - this auxiliary request had in fact been filed only at the oral proceedings.

57. As regards appellant I's second argument that the board in its communication had not taken up any of the other

objections raised by the opponent-appellants (which could potentially apply to the now claimed subject-matter), it is noted that a board is not obliged to give a preliminary opinion on each and every objection raised in the appeal proceedings. A communication under Article 15(1) RPBA serves as guidance for the oral proceedings. In accordance with this purpose a board may in such a communication (see Article 15(1) RPBA) draw *"attention to matters which seem to be of special significance, or to the fact that questions appear no longer to be contentious, or containing other observations that may help concentration on essentials during the oral proceedings."*

58. Furthermore, in addition to appellant I's arguments, the board, when deciding on the admissibility of auxiliary request 35, has taken into account criteria developed by the case law in relation to the admissibility of claims submitted for the first time during oral proceedings. For example, a claim request submitted at a late stage might be allowable if its submission can be considered an appropriate reaction to unforeseeable developments in the proceedings or if it would be immediately apparent to the board, with little or no investigative effort on its part, that the new request is clearly and obviously allowable (see Case Law of the Boards of Appeal, 8th edition 2016, section IV.E.4.2.6 a)).

59. In the present case, the filing of the auxiliary request was a reaction to the board's finding that the "combination feature" did not meet the requirements of Article 123(2) EPC. This finding however could not be considered unforeseeable or unexpected, given that it was in line with the board's preliminary opinion set

out in its communication issued pursuant to Article 15(1) RPBA.

60. Furthermore, it was in fact immediately apparent to the board that this request could not be considered clearly and obviously allowable, as there were a number of outstanding added subject-matter objections which had been raised by the opponent-appellants in their respective statements of grounds of appeal and which had not been addressed by the amendments made (see also section XII).
61. Lastly, the reasons why appellant I did not file (what is now) auxiliary request 35 with its reply to the statement of grounds of appeal, i.e. the wish to address the issues of the appeal with a reasonable number of claim requests and the wish to take account of added subject-matter issues that had been of concern to the board in the parent case T 1536/14 and of which the "combination" objection was not a part, can also not convince the board that the appropriate time for filing auxiliary request 35 would have been in reply to the board's communication. This is so in view of the fact that the "combination" objection was an issue in the present appeal from the beginning (see section VII).
62. Therefore, in view of all the above considerations, the board decided not to admit auxiliary request 35 into the proceedings in accordance with Article 114(2) EPC and Article 13(1) RPBA.

Conclusion

63. In the absence of an allowable claim request, the patent is to be revoked.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar:

The Chairwoman:



P. Cremona

G. Alt

Decision electronically authenticated