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Datasheet for the decision of 10 October 2022

Case Number: T 2585/18 - 3.3.04

Application Number: 11180259.1

Publication Number: 2409707

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Language of the proceedings: EN

Title of invention:
Polymer-based sustained release device

Patent Proprietor:
Alkermes Pharma Ireland Limited
Amylin Pharmaceuticals, LLC

Opponents:
PHARMATHEN S.A.
Teva Pharmaceutical Industries Ltd.

Headword:
Exendin-4 sustained release composition/ALKERMES

Relevant legal provisions:
EPC Art. 100(a), 54, 56, 100(b), 100(c)

Keyword:
Added subject-matter (no)
Novelty - main request (yes)
Insufficiency of disclosure (no)
Inventive step - (yes)

Decisions cited:
T 0435/91, T 1697/12, T 1320/13, T 0061/14

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Case Number: T 2585/18 - 3.3.04

D E C I S I O N
of Technical Board of Appeal 3.3.04
of 10 October 2022

Appellant: (Patent Proprietor 1)	Alkermes Pharma Ireland Limited Connaught House 1 Burlington Road Dublin 4 (IE)
Appellant: (Patent Proprietor 2)	Amylin Pharmaceuticals, LLC 9360 Towne Centre Drive San Diego, CA 92121 (US)
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Party as of right: (Opponent 2)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	Lederer & Keller Patentanwälte Partnerschaft mbB Unsöldstraße 2 80538 München (DE)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 July 2018 concerning maintenance of the European Patent No. 2409707 in amended form.**

Composition of the Board:

Chairwoman M. Pregetter
Members: O. Lechner
C. Almberg

Summary of Facts and Submissions

I. Appeals of the patent proprietors and opponent 1 lie from the opposition division's decision that European patent No. 2 409 707 ("the patent"), amended in the form of auxiliary request 3 (as filed during oral proceedings), and the invention to which it relates, meets the requirements of the EPC.

II. The patent is based on European patent application No. 11 180 259.1, a divisional application of European patent application No. 04 750 134.1, which had been filed as an international application and published as WO 2005/110425.

III. Claim 1 as granted reads as follows:

"1. A composition for sustained release of a biologically active polypeptide, comprising a biocompatible polymer having the biologically active polypeptide dispersed therein so as to be present at 3% (w/w) to 10% (w/w) of the weight of the composition, and sucrose dispersed therein so as to be present at 2% (w/w) of the weight of the composition,

wherein the biologically active polypeptide is exendin-4,

wherein a total pore volume of the composition is 0.1 mL/g or less as determined using mercury intrusion porosimetry and

wherein the composition is free from buffer and salting-out salts."

IV. The patent was opposed on the grounds set out in Article 100(a), for alleged lack of novelty (Article 54 EPC) and of inventive step (Article 56 EPC), and (b) and (c) EPC.

V. In the decision under appeal, the opposition division decided that the main request (claims as granted) and auxiliary request 1 lacked an inventive step. Auxiliary request 2 was held to not comply with the requirements of Rule 80 EPC. The patent was maintained on the basis of the set of claims according to auxiliary request 3 (as filed during oral proceedings).

VI. Opponent 2 is a party as of right to the appeal proceedings. It made no substantive submissions during the written appeal proceedings.

VII. The board summoned the parties to oral proceedings as requested and informed them of its preliminary opinion in a communication pursuant to Article 15(1) RPBA 2020.

In this communication the board indicated that:

- claim 1 of the main request finds basis in the application as filed;
- the subject-matter of claim 1 was novel over the disclosure in document D1;
- the patent disclosed the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art; and
- document D2 appeared to be the closest prior art for assessing inventive step.

VIII. Oral proceedings before the board took place on 10 October 2022 in the form of a videoconference. At the end of the oral proceedings, after the final

requests had been established, the Chairwoman announced the board's decision.

IX. The following documents are cited in the present decision:

D1 : WO 2004/034975 A2

D2 : WO 03/020245 Al

D6 : European Pharmacopoeia 07/2008:20932; 2.9.32. Porosity and pore-size distribution of solids by mercury porosimetry, 3643-5

D7 : P.A. Webb, An Introduction To The Physical Characterization of Materials by Mercury Intrusion Porosimetry with Emphasis On Reduction And Presentation of Experimental Data; Micromeritics Instrument Corp. Norcross, Georgia, January 2001, 24 pages

D8 : Y. Yeo et al., Arch Pham Res, Vol. 27(1), 2004, 1-12

D9 : J.C. Lee, J Biol Chem, Vol. 256(14), 1981,7193-7201

D16: Annex-1, Plot of in vitro burst, based on data in Table 2 of the patent, filed by the patent proprietor with the letter of 26 July 2016, 1 page

D17: AutoPore^{TM} IV Series, Automated Mercury Porosimeter, product brochure, 6 pages

D19: Experimental report, submitted by opponent 1 with the letter of 4 August 2017, 7 pages

D21: raw data sample by patent proprietors; filed by the patent proprietors with the letter of 4 August 2017, 18 pages

X. In the following, the parties are identified by their roles in the opposition proceedings.

XI. The patent proprietors' arguments, relevant to the decision, are summarised as follows.

Main request - patent as granted

Amendments - Article 100(c) EPC

The features of claim 1 found basis in the application as filed as follows:

- *Exendin-4 as the glucoregulatory polypeptide*:
  Exendin-4 was unquestionably the preferred peptide throughout the entire application.

- *3 to 10% (w/w) exendin-4*:
  This range was the result of limiting the range of about 0.1% to about 10% (w/w) with the lower limit of 3% which was identified as providing "*superior release profiles*". All these features were provided on page 7, lines 9 to 12 of the application as filed. The reported superior release profile provided a clear pointer to select the 3% as an end point. This was not an arbitrary selection.

- *The sugar selected is sucrose*:
  Sucrose was evidently the preferred sugar. Page 7, lines 29 to 30 stated that "*Excellent release profiles were obtained incorporating about 2% (w/w)*

sucrose", directing the skilled person towards a composition comprising 2% sucrose.

Disclosure of the invention - Article 100(b)

In the following, opponent 1's objections are rebutted.

(a) *Total pore volume (TPV) was an unusual, inadequately defined parameter*

The objection to the meaning of the term "total pore volume" was a clarity objection under Article 84 EPC, which was not a ground for opposition.
TPV was neither a new nor an unfamiliar parameter. Opponent 1 itself had pointed to numerous documents which discussed TPV and explained how to measure the volume of pores in particles and distinguish this from the volume of spaces between particles (see, for example, document D7).

The skilled person knew that the volume of pores in microparticles was relevant for the release of drug from microparticles and thus was what the skilled person measured when calculating TPV according to the invention. Therefore, the skilled person could identify compositions in which the TPV of pores was 0.1 ml/g or less.

The measurement of pore volume in document D19 included the interstitial volume, which a skilled person would not include.

(b) *There were no examples of microparticles with a TPV of 0.1 ml/g or less and lack of any teaching in the patent on how to ensure that a TPV of 0.1 ml/g or less could be achieved*

The patent stated in paragraph [0091] that the batches for which the TPV values are provided were made using the method described in the patent. Opponent 1 had argued that if the skilled person followed the patent proprietor's interpretation, the values obtained would be different from the values in Tables 1 and 2 of the patent. If opponent 1's arguments were followed, the actual TPV would be even lower than the values in the table.

Document D19 provided experimental data attempting to show that only TPVs > 1.0 ml/g could be obtained by following the method described in the patent. However, in the experiments provided in document D19, opponent 1 had failed to follow the protocol for producing microparticles as described in the patent.

There was ample evidence in the patent that the skilled person was capable of obtaining the claimed compositions. Opponent 1 had not provided credible evidence to raise any doubts that this was the case. Thus, its objections had to be dismissed.

(c) *claim 1 included subject-matter yet to be enabled or invented, i.e., compositions with zero porosity*

The skilled person seeking to put the invention into practice would not consider using a composition having zero porosity. It was clear from the patent that porosity was a crucial factor affecting the release of exendin-4 and that the presence of this porosity was an essential element of the invention. The fact that the patent did not describe how to prepare zero porosity compositions was therefore irrelevant.

(d) *Format of the composition*

Reference was made to the opposition division's decision on this issue and that opponent 1 had failed to address the opposition division's reasoning in appeal.

Novelty - Article 100(a) and 54 EPC

Document D1 disclosed two PLG (poly(lactide-co-glycolide)) microparticle compositions on page 25, lines 6 to 11 which were not novelty-destroying because the exendin-4 and sucrose concentrations fell outside the claimed ranges.

Inventive step - Article 100(a) and 56 EPC - claim 1

Closest prior art
Document D2 represented the closest prior art.

Difference, its technical effect and the technical problem to be solved

The subject-matter of claim 1 differed from the disclosure in the closest prior art, document D2, by three features:

i) the presence of 3 to 10% exendin-4
ii) the presence of 2% sucrose
iii) the lack of a buffer and salting-out salts

In addition, document D2 did not provide any TPV value for the microparticles produced according to the methods disclosed.

The plotted data of the patent, as shown in document D16, confirmed this correlation between TPV and the *in vitro* burst rate.

The three technical differences all had their own technical effect(s) that worked together to provide the sustained release formulation with an improved release profile.

The technical problem was how to reduce the total quantity of an exendin-4 sustained release composition for administration while achieving low initial burst.

Obviousness

Each difference was linked to its own technical effects not derivable from document D2 or any other prior art. Document D2 established no correlation between low TPV and low initial release rate.

Document D8 described double emulsion process problems, i.e., problems of a very different process of producing the sustained release composition, and thus would not have been considered by the skilled person. On page 6, left-hand column, drug distribution and the morphology of the microparticles were discussed as potential causes of initial burst release. However, as evidenced by the first sentence of the first full paragraph on the right-hand column of the same page, it was not known what the essential parameter was. This became clear when reading Table IV on page 10 of document D8, which provided five possible strategies for reducing the initial burst, none of them relating to TPV.

The claimed sustained release composition was not obvious from closest prior art document D2, either alone or in combination with documents D8 and/or D9.

XII. The opponents' arguments, relevant to the decision are summarised as follows.

Main request - patent as granted

Amendments - Article 100(c) EPC

There was added matter arising from the combination of 3% (w/w) as an end-point of a new range in "biologically active polypeptide dispersed therein so as to be present at 3% (w/w) to 10% (w/w) of the weight of the composition". This selection represented an arbitrary selection of exendin-4 levels.
Decision T 1320/13 made clear that it was not possible to combine individual values with values from a range.

Disclosure of the invention - Article 100(b)

(a) TPV was an unusual, inadequately defined parameter

The claimed composition could clearly comprise a plurality of microparticles as also set out in the patent (see paragraph [0091]). From the teaching in documents D6 (see page 3643, right-hand column, paragraph 2 in chapter 2.9.32; page 3644, left-hand column, paragraph 2; page 3645, right-hand column, paragraph 4), D7 (see page 8, left-hand column, chapter "*Total Pore Volume*"; right-hand column first full paragraph; page 9, right-hand column, paragraphs 2 and 3) and D17 (see page 4, first figure; page 5, "Intrusion Data Summary" box), it was evident that the

term "total pore volume" was equivalent to "total intrusion volume", which was the total volume of mercury required to fill all accessible pores as the pressure of mercury is increased from its minimum value up to the maximum pressure available. Both inter-particles pores (pores formed by the spaces between particles) and intra-particle pores (pores due to voids within a particle) were included in the TPV.

Inter-particles and intra-particle pore volume were both treated as pertaining to pores and could only be distinguished if the two types of pores differed in size without overlap. The data in document D17 showed that it was not possible to distinguish where inter-particles pores end and intra-particle pores start.

The definitions in the patent for TPV (see paragraphs [0007] to [0009], [0038], [0089] and [0092] did not depart from the conventional interpretation of "total pore volume", i.e. did not indicate that it was essential to manipulate the mercury intrusion data to eliminate the intrusion volume associated with inter-particles pores.
There was nothing in the patent about obtaining a TPV value, from the measured (total) pore volume by subtracting the volume arising from the mercury being forced into the pores of the porous bed of microparticles.

Thus, a reader of the patent would:

i) not understand that "total pore volume" was intended to mean "intra-particle pore volume" only, and
ii) not know from the patent/the application as filed, how to distinguish between inter-particles and intra-

particle pores measured for the claimed compositions over the entire claimed scope

The omission of this essential step from the application as filed/patent - the requirement to manipulate the mercury intrusion data to remove the inter-particles pore volume from the TPV - meant that it was impossible for the skilled person to put the claimed subject-matter into practice, no matter how they modified the preparation methods set out in the patent.

(b) There were no examples of microparticles with a TPV of 0.1 ml/g or less and a lack of any teaching in the patent on how to ensure that a TPV of 0.1 ml/g or less could be achieved

Document D19 showed that by following the process set out in the patent but using other biodegradable polymers within the scope of claim 1, TPVs greater than 0.1 ml/g were achieved, irrespective of whether the measured TPV included inter-particles spaces, which were large; the pore volume relating solely to internal pores of microparticles; or the arbitrary range of pores 3 µm or smaller in size, as described in document D21, but not specified in the patent.
Thus, following the teachings on the examples in the patent would not necessarily lead to a composition with a TPV of 0.1 ml/g or less, irrespective of which definition for TPV was used.

(c) Claim 1 included subject-matter yet to be enabled or invented, i.e. compositions with zero porosity

The scope of claim 1 encompassed compositions for which the porosity was 0.00 ml/g. The examples in the patent

only had so-called TPV down to 0.03 ml/g (and that value was in a comparative example with ammonium sulphate present).

There was no suggestion in the patent on how to even start to try to achieve zero porosity.

Furthermore, the patent did not show how to prepare microparticles with a diameter of 1 µm (see paragraph [0033] of the patent). For particles of that size there was an overlap between inter-particles voids and intra-particle pores, such that TPV as defined by the patent proprietor, became unmeasurable.

Document D6, page 3644 taught that "*Inter-particle and intra-particle porosity can be determined, but the method does not distinguish between these porosities where they co-exist*".

(d) Format of the composition

Considering the definition of TPV in claim 1 and the methods disclosed in the description, formulations not being in particulate form could only be obtained by compression.
However, there was no enabling disclosure on how films, pellets, cylinders, or discs falling within the scope of claim 1 (see also claim 5) could be obtained.

Novelty - Article 100(a) and 54 EPC

The process used in the Example SF-2 of document D1 was identical to the process used in the examples of the patent and so had to inherently give the same TPV when applied to the same compositions. SF-2 had thus all the

technical features of claim 1 of the main request. In addition, it included ammonium sulphate, a salting-out salt excluded from the subject-matter of claim 1 as amended.

However, when considering novelty, it was the whole content of a document that had to be assessed. On page 24, last paragraph document D1 provided as clear alternative options that the exendin-4 was to be combined either with sucrose or sucrose and ammonium sulphate. SF-2 used sucrose and ammonium sulphate together, but the alternative, i.e., just sucrose, was also directly and unambiguously disclosed in document D1.

Inventive step - Article 100(a) and 56 EPC - claim 1

Closest prior art

Document D2 represented the closest prior art.

Difference, its technical effect, and the resulting technical problem

The sustained release composition according to claim 1 differed from the one in Example 9, Batch 4, of document D2 with regard to three properties:
i) the presence of 3 to 10% exendin-4
ii) the presence of 2% sucrose
iii) the absence of a buffer and salting-out salts

The patent and Example 9 of document D2 used essentially the same process for producing the exendin-4 comprising microparticles. Thus, it had to be

assumed that TPVs within the same range were obtained by the two methods.

There was no evidence in the patent of an improved technical effect due to one or more of these differing properties. In addition, there was no comparison with the closest prior art.

No synergistic effects due to the combination of two or more of these parameters had been shown. Thus, their effect had to be evaluated separately.

The burden of proof was on the patent proprietors to show that there was a technical effect.

The technical problem could be defined as the provision of a sustained release composition with a low initial burst.

Obviousness

Starting from the teaching of closest prior art document D2, the claimed composition was obvious to the skilled person.

Apart from the fact that an unclear parameter, such as TPV, could not be used to differentiate over the prior art, document D8 disclosed that protein release from poly (lactic-co-glycolic acid (PLGA) microparticles during the initial release stage depended on diffusional escape through pores and cracks existing in the polymer matrix (see especially page 7, right-hand column, paragraph 2 and page 10, right-hand column, last paragraph).

Thus, combining the closest prior art disclosure with the teaching of document D8 rendered it obvious to reduce TPVs to achieve a reduced initial burst. No benefits had been shown for the claimed sucrose and exendin-4 concentrations combined with the absence of a buffer and salting-out salts. The claimed technical features were either known from document D2 or the state of the art and thus obvious.

XIII. Requests of the parties

The patent proprietors requested that
- the appealed decision be set aside and that the patent be maintained as granted (main request), or
- that opponent 1's appeal be dismissed (i.e., that the patent be maintained based on auxiliary request 3 as decided by the opposition division).

Opponent 1 requested that
- the appealed decision be set aside and that the patent be revoked, or, otherwise,
- that the proprietors' appeal be dismissed.

Opponent 2 requested that
- the proprietors' appeal be dismissed.

Reasons for the Decision

Main request

Amendments - Article 100(c) EPC

1. The descriptions of the parent and divisional applications as filed are identical. In the following reference is made to the description of the parent application as published (WO 2005 110 425).

2. The board agrees with the opposition division's decision that claim 1 of the main request complies with Article 100(c) EPC.

2.1 Page 10, last paragraph to page 11, paragraph 1 provides a "*sustained release composition* [that] *comprises a biocompatible polymer, a biologically active polypeptide and a sugar wherein the composition has a total pore volume of about 0.1 mL/g or less. In a specific embodiment, the total pore volume is determined using mercury intrusion porosimetry* [...]".

2.2 Exendin-4 as biologically active polypeptide:

The description provides on page 5, line 22 to page 11, line 2 detailed information on the components which can be present in the sustained release compositions of the invention. Page 5, line 25 to 26 mentions that "[m]*ost specifically, the polypeptide is exendin-4*". Moreover, as argued by the patent proprietors, exendin-4 is the polypeptide used in all examples (see microparticle preparation I and II) and the only one discussed in detail in the description (see page 6, line 18 ff). Moreover, the passage on page 7, lines 3 to 12 only

mentions exendin-4 as a possible biologically active polypeptide. Thus, the skilled person would have directly and unambiguously derived that exendin-4 is the most preferred biologically active polypeptide throughout the application, i.e. no selection is necessary.

2.3 *3 to 10% (w/w):*

The claimed range of 3 to 10% (w/w) of the biologically active polypeptide can be obtained by combining the lower end point of the preferred range of about 0.1 to about 10% (w/w) with the value of 3% (w/w), which falls within the preferred range (see page 7, lines 9 to 12).

2.3.1 The decisive question is, would the skilled person have derived the newly created range from the disclosure in the application?
Page 7, first full paragraph provides the preferred range of 0.1% to 10% but also the information that "[s]*uperior release profiles were obtained when the agent, e.g. exendin-4, was loaded at about 3% w/w*".

2.3.2 The skilled person, when cutting down the preferred range of 0.1% to 10%, would have considered the value described to result in superior release profiles, i.e., 3% (see page 7, lines 11 to 12). No selection from a list of equivalent alternatives is necessary in this case.

2.3.3 In decision T 1320/13, the board held (see Reason 13, first argument) that a range necessarily encompassed all the values that lay between its two disclosed end-points, whereas a list of individually disclosed values (cf. Reason 12) did not encompass the values that lie between them.

In line with T 1320/13, the range in the current case, of 0.1% to 10% (w/w) encompasses all the values lying between the end-points, including 3%.

However, unlike in decision T 1320/13 (see Reason 13, second argument), the present application contains a clear pointer to the value of 3% (w/w) exendin-4 as it is reported to lead to better release profiles (see above). This value can thus serve to limit the range by serving as an end-point.

2.4 *The sugar is sucrose:*
The description emphasises on page 7, lines 29 to 30 that "[e]*xcellent release profiles were obtained incorporating about 2% (w/w) sucrose*" into the sustained release composition. Compositions comprising 2% (w/w) sucrose are thus preferred. Furthermore, all examples, irrespective of their exendin content, contain 2% (w/w) sucrose.

2.5 Basis for the absence of a buffer and salting-out salts in the claimed composition can be found on page 10, lines 25 to 27.

2.6 The amendments thus result from an allowable combination of preferred features and do not extend beyond the content of the application as filed or beyond the content of the earlier application as filed.

Disclosure of the invention - Article 100(b)

3. In the following, several aspects are discussed which are crucial for the assessment of sufficiency of disclosure. The aspects are dealt with as brought forward by opponent 1.

(a) *TPV was an unusual, inadequately defined parameter*

3.1 The board agrees with the patent proprietors and the opposition division that the skilled person knew what "total pore volume" (TPV) means and how to determine it.

Document D7, page 8, left-hand column provides a clear definition of TPV as being the volume of mercury required to fill all accessible pores, determined at the maximum pressure. On the same page, right-hand column, the term "envelope volume" is coined to define "*the sum of the volumes of the solid components, the open and closed pores within each piece, and the voids between the surface features of the material and the close-fitting imaginary film that surrounds the piece*". On page 9, right-hand column, the term "interstitial void volume", also called "inter particle void", which is the space between packed particles is explained. Furthermore, it is stated that the "*completion of interparticle void volume filling is indicated by an abrupt change in filling rate observed on the intrusion curve. The total volume of the interparticle voids is* the volume of *mercury intruded at the inflection point".*
Hence, document D7 clearly distinguishes between the intra-particle volume and the inter-particles volume.

Thus, mercury intrusion porosimetry was a well-known technique for determining the porosity in the state of the art. Consequently, the patent does not need to provide a detailed description of this method.

3.2 A skilled person understood a "pore" as an opening in a surface. In contrast, inter-particles spaces are defined as "interstitial void volumes" or "voids". Thus, the term total pore volume (TPV) can only mean the totality of the volumes of individual pores present in a body. Based on the teaching in document D7 (see above and in particular on page 9, right-hand column, paragraph 2) it was technically possible to measure and to distinguish TPV from interstitial void volumes using mercury porosimeter readings.

3.3 Opponent 1 argued that for particles with a diameter of 1 µm, there was an overlap between inter-particles voids and intra-particle pores, such that the TPV, as defined by the patent proprietor, became unmeasurable.

The board considers that when working with microparticles within the lower region of the diameter range suggested in paragraph [0033] of the patent, the skilled person would adjust the parameters of the porosity measurement to be able to distinguish the TPV from the inter-microparticles voids also in such cases. Should overlap occur in borderline cases, the measured TPV, potentially also comprising inter-particles voids, would be less than or equal to 0.1 ml/g according to claim 1. In such cases, the actual TPV of the intra-particle pores would be even lower and thus necessarily below the 0.1 ml/g threshold.

3.4 Opponent 1 also referred to document D6 as indicating that TPV encompassed intra-particle pores as well as

inter-particles voids. Reference was made to page 3643, right-hand column, paragraph 4, which disclosed that porosity and pore-size distribution can be measured by mercury porosimetry, and to page 3644, left-hand column, paragraph 2, which stated that "*Inter-particle and intra-particle porosity can be determined, but the method does not distinguish between these porosities where they co-exist*".

However, from the board's understanding of D6, page 3645, right-hand column, paragraph 4 also clarifies that it is possible to separate the space between the particles (voids) from the particles' pores. Hence, the teaching in document D6 does not contradict the teaching in document D7.

Paragraph [0089] of the patent provides some basic information on how to measure the pore volume using a mercury intrusion porosimeter. The method described is consistent with the one disclosed in document D7, as discussed above.

Thus, TPV was a common parameter used in in the art to describe the porosity of solid parts of a composition.

3.5 Some of opponent 1's arguments on TPV relate to an assessment of lack of clarity (Article 84 EPC), which is not a ground for opposition and thus cannot be dealt with. One of the issues addressed by opponent 1 is the clear separation of inter-particles voids/pores and intra-particle pores in all instances.

(b) *Lack of any teaching in the patent on how to ensure that a TPV of 0.1 ml/g or less could be achieved, and there being no examples of microparticles with a TPV of 0.1 ml/g or less*

3.6 Table 2 clearly shows that the batches according to the invention have TPVs well below 0.1 ml/g (see, e.g. Lot# 2, 2-1 and 2-2 to 2-5).

Opponent 1 referred to its post-published data in document D19, which was an attempt by opponent 1 to reproduce the claimed subject-matter.

The data presented in document D19 allegedly showed that following the protocol set out in the patent and using other biodegradable polymers, within the scope of claim 1, only TPVs > 0.1 mg/l could be obtained. However, the board agrees with the opposition division (see decision point 72) that the experimental protocol in document D19 is in many respects less detailed than, and also differs from, the protocol described in the patent.

3.7 In the coacervation step of the patent, silicone oil is added over about 3 to 5 minutes (see paragraph [0081]), whereas in document D19 this is done within 2 to 3 minutes (see page 1, last paragraph).

Compared to the patent, document D19 (see page 2, paragraph 2) is also less detailed on how the internal water-in-oil emulsion was formed (compare paragraph [0080] with D19, page 1, paragraph 4) and how the microspheres were dried (compare paragraphs [0083] to [0085] of the patent with document D19, page 2, paragraph 2).

Thus, the data in document D19 are not directly comparable with those in the patent and do not allow the conclusion that the examples of the patent in suit do not result in TPVs below 0.1 ml/g, as set out in

e.g. Table 2 of the patent.

The patent contains a teaching on how to tackle the (potential) failure of document D19 to obtain the required TPV. It is suggested to use a ratio of dimethicone to methylene chloride of 1.5:1 in the preparation of the microparticles (see paragraphs [0069] and [0079]), whereas a ratio of 1:1 was chosen for the experiments in document D19. As indicated in paragraph [0094] of the patent, a higher ratio of silicone oil to methylene chloride results in lower porosity and a lower *in vitro* burst.

(c) *Claim 1 included subject-matter yet to be enabled or invented, i.e. compositions with zero porosity*

3.8 Again, the board agrees with the opposition division's findings (see point 74 of the decision), that it is clear from the patent that TPV is a crucial factor affecting the release of exendin-4 and that the presence of this parameter is an essential element of the invention. The skilled person trying to put the invention into practice would therefore not consider using a composition having zero porosity. Thus, opponent 1's argument that the patent did not teach the skilled person how to make a composition with zero porosity is not relevant.

3.9 The opponent referred to decisions T 435/91, T 1697/12 and T 61/14 as supporting its argumentation.

3.9.1 T 435/91 cannot support opponent 1's argument since it does not concern open-ended ranges.

3.9.2 In T 1697/12, claims 1 and 2 referred to a water absorbing agent being *inter alia* characterised by upper

open ended ranges of absorbency values and their ratios. The highest ranges covered embodiments that could not be obtained with the process disclosed in the patent, as also admitted by the patent proprietor. It explained that no upper limit had been included in the claim since it was clear that water-absorbent agents with increased absorbency would be invented in the future. The board decided that the sufficiency requirements were not met given that the patent monopoly should not be extended to subject-matter which, after reading the patent specification, would not yet be at the disposal of the skilled person (see Reasons 5.1 and 5.5).

The current case differs from this decision in that, as stated in point 3.8 above, the skilled person would not have considered working in the allegedly unobtainable parts of the claimed range.

3.9.3 In T 61/14, the board found that the embolisation particles of claim 1 of all requests were not disclosed in a manner sufficiently clear and complete. Claim 1 was directed to an embolisation particle comprising "interconnected pores that extend to the surface of the particle, wherein at least 20% of the pores are interconnected", i.e. the claim covered a closed range from 20% to 100%. Examples 1 to 4 of the patent in suit had a percentage of interconnected pores close to 100% (see Reason 5.3). There was however not any evidence showing that, at the filing date, it was generally known to a person skilled in the art how to modify the percentage of interconnected pores of the particles (see Reason 5.6). Moreover, the patent did not disclose how to measure the percentage of pores which are interconnected (see Reasons 5.7 to 5.10).

In the case at hand it has been established that TPV was a parameter which could be measured by the skilled person using mercury porosimetry.

3.9.4 Thus, none of the circumstances leading to the above decisions is comparable with the current situation. As stated in 3.8 above, while the claim theoretically includes a TPV of 0 ml/g, the skilled person would have considered extremely low TPV values (i.e. values in the vicinity of zero) to be excluded by the definition of the composition to provide a sustained release of a biologically active polypeptide.

(d) *Format of the composition*

3.10 The board agrees with the opposition division (see decision point 76) that for the skilled person there is no apparent undue burden to prepare the claimed composition in any other form than microparticles, e.g. a disc or film.
The alternative galenic forms described in the description are, in general, obtainable by various processes including processes not relying on compaction. Furthermore, opponent 1 has provided no evidence that compaction leads to a change in TPV. Consequently, the opponent has failed to substantiate its objection by verifiable facts as required by the case law (see Case Law of the Boards of Appeal, 10th ed., 2022, III.G.5.1.2.c)).

3.11 Consequently, the board considers that the patent discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

Novelty - Articles 100(a) and 54 EPC

4. Document D1 discloses composition SF-2 comprising, in addition to the biocompatible polymer, 3% exendin-4, 2% sucrose, and 0.5% ammonium sulphate, i.e. a salting-out salt. Due to, at least, the presence of the salting-out salt, this composition cannot destroy the novelty of the claimed subject-matter.

5. Composition IF-1, although being free of salting-out salt, contains a buffer. In addition, it does not comprise exendin-4 and sucrose in the required amounts.

6. Opponent 1 pointed to document D1, page 24, lines 28 to 30, as teaching compositions comprising exendin-4 and sucrose free of ammonium sulphate. According to opponent 1 this disclosure had to be taken into account under the "whole contents" approach.

The board cannot agree. There is no direct and unambiguous disclosure that such an alternative composition would be prepared with the amounts of exendin-4 and sucrose claimed. As can be seen from the composition IF-1, other amounts of exendin-4 and sucrose were also exemplified. In addition, the passage in document D1 on page 24, lines 28 to 30, offers as an additional selection the dissolution of exendin-4 and sucrose in an aqueous buffer, which necessitates a further selection.

Thus, document D1 does not anticipate the subject-matter of claim 1 (Article 54(3) EPC).

Inventive step - Articles 100(a) and 56 EPC - claim 1

Closest prior art

7. The board agrees with the parties that document D2 represents the closest prior art.

Document D2 relates to controlled release microparticles and discloses in paragraph [0110] a "Batch 4" formulation of microparticles comprising about 1% AC2993 (= exendin-4, see document D9) and about 1% sucrose in an acetate buffer pH 4. While the same chemical substances were used as in the patent in suit, the latter uses, for example, different sonication conditions during the emulgation step.

In the patent, the water phase was added to the oil phase over about a three-minute period while sonicating at 100% amplitude at ambient temperature. The reactor was then stirred at 1400 to 1600 rpm, with additional sonication at 100% amplitude for 2 minutes, followed by a 30-second hold, and then 1 more minute of sonication (see page 9, paragraph 78).

In the method of document D2, the aqueous phase was added to the oil phase using a syringe/needle and sonicated for 1 minute. Sonication was repeated twice with a 3 minutes gap in-between. The resulting emulsion was transferred into a coacervation reactor and stirred at 1617 rounds per minute (rpm) using an impeller (see paragraph [0110]).

Due to these differences, it is not possible to conclude with certainty that the resulting TPV of the microparticles prepared according to the protocol disclosed in document D2 falls within the claimed

range. Thus, the resulting TPV in the microparticles prepared in document D2 is not known.

Difference, its effect and the objective technical problem

8. As agreed upon by the parties, the subject-matter of claim 1 differs from the "Batch 4" preparation in document D2 in that its composition:

i) comprises 3 to 10% (w/w) exendin-4 (instead of about 1% exendin-4);

ii) comprises 2% (w/w) sucrose (instead of about 1 % sucrose);

iii) lacks a buffer and salting-out salts (while "Batch 4" of D2 contains an acetate buffer pH 4);

According to claim 1 the composition has a TPV of 0.1 ml/g or less. Document D2 does not disclose any values for the TPV of its microparticles.

8.1 i)

The board agrees with the patent proprietors that a higher amount of active agent per unit weight of drug composition is beneficial because less drug composition needs to be administered to provide the same dose.

8.2 ii)

The technical effect of the 2% sucrose lies in the stabilisation of the 3 to 10% exendin-4.
It is clear from the data of the patent in suit, see Figure 6, that the addition of sucrose, while

undisputedly stabilising exendin-4, leads to a higher initial burst.

8.3 iii)

As for the absence of a buffer and salting-out salts, the technical effect can be seen in providing a composition that is easier to prepare, i.e. as the patent proprietors put it, "more straightforward", yet that still produces the desired sustained release of exendin-4.

The patent also reports in paragraph [0095] (see also Figure 1 and Table 1 and 2) that "*Formulations made with ammonium sulfate showed varying levels of in vitro release and variable porosity unlike formulations without ammonium sulfate which exhibited consistent porosity and release*".

8.4 TPV

The data in Tables 1 and 2 of the patent show that microparticle batches with a TPV of 0.1 ml/g or less, e.g. batch #3-6 exhibit significantly lower *in vitro* burst compared to those with a TPV of more than 0.1 ml/g, e.g. batch #3-7 with a TPV of 0.180 ml/g. Although this effect is only shown for microparticles comprising ammonium sulphate, no reasons have been presented why this effect should not arise with microparticles according to claim 1. The opponent has addressed the higher initial burst of batches #2-3 to 2-5 compared with batches #2, 2-1 and 2-2, which, according to the opponent was due to a different ratio of silicone oil to methylene chloride while the TPV values were similar. The board, while agreeing with the opponent's

finding in theory, notes that the initial burst values of these batches have the same order of magnitude.

8.5 The patent shows that the claimed combination of features i) to iii) and a TPV of less than 0.1 ml/g results in a sustained exendin-4 release composition with a low initial burst.

9. The objective technical problem is the provision of an exendin-4 sustained release formulation with a low initial burst.

Obviousness

10. The board is of the opinion that starting from the disclosure of document D2, the claimed subject-matter would not have been obvious for a skilled person.

10.1 i) 3 to 10% exendin-4
It would have been obvious, as stated by the patent proprietors, that a content of (a) 3 to 10% exendin-4 allows for a greater drug load per weight unit compared to Batch 4 disclosed in document D2 containing about 1% exendin-4, allowing the administration of a smaller total volume/quantity of the drug composition.

The board agrees with opponent 1 that it would also have been obvious to vary the level of active agent depending upon the equilibrium plasma levels desired. This is in line with the general suggestion in document D2 that higher amounts of an active agent may be loaded (see paragraph [0115]). Furthermore, it is well established that smaller unit dosage forms are more readily accepted by patients and thus lead to improved patient compliance.

Taking merely the increase in exendin-4 into account can thus not establish the presence of an inventive step.

10.2 ii) 2% sucrose

As argued by opponent 1, the protein-stabilising effect of sucrose was known in the art (see e.g. document D9). However, the board agrees with the patent proprietors that starting from the composition of document D2, comprising 1% exendin-4 and 1% sucrose, it was not known or derivable from the teaching of document D9, how much sucrose needed to be added to stabilise the higher concentration of 3 to 10% exendin-4. The skilled person could have, while carrying out routine experiments, opted for keeping the ratio of sucrose to active peptidic agent lower than in document D2.

It has, however, to be kept in mind that the objective technical problem, reflecting the aim of the patent in suit defined by claim 1, requires the provision of a sustained release composition of a pharmaceutically active peptidic agent. This implies that the active peptidic agent is stable throughout the time needed for complete release.

10.3 iii) Absence of a buffer and salting-out salts

The board agrees with the patent proprietors that document D2, the only document in the prior art describing an exendin-4 formulation similar to the one of the patent, does not comprise any pointer that the buffer may be omitted when preparing the biodegradable polymers described in Example 9, Batch 4. Starting from the example of document D2, the person skilled in the art had no incentive to leave out a component, i.e. the

buffer used to adjust the composition to pH 4. It is well established that the pH of compositions comprising peptidic agents is crucial to the stability of these agents.

10.4 TPV

The patent shows that a TPV of 0.1 ml/g or less results in a reduced initial release of exendin-4 from biocompatible polymers.

The patent does not compare the claimed exendin-4 microparticle formulation with the one disclosed in the closest prior art document D2. However, this is not considered necessary in the current case as document D2 does not discuss the release pattern of the microparticles produced by the method(s) disclosed in it. The focus on D2 is on minimising residual solvents.

Opponent 1 argued that document D8 disclosed the context between a high porosity of PLGA microparticles and an undesired initial burst.

However, document D8 discusses several strategies for minimising the undesired initial burst. On page 6, starting at the left-hand column, last two paragraphs, it is disclosed that "*First, burst release occurs mainly due to the heterogeneous drug distribution [...] Second, morphology of the microparticles causes initial burst. The drugs escape from the polymeric matrices through the pores and cracks that form during the microparticle fabrication process*". In the third paragraph of this chapter, it is further explained that "*It is likely that both causes contribute to the initial burst, although their relative contributions are yet to be determined*". Five possible strategies for

reducing the initial burst are also provided in Table IV. on page 10, none of them addressing the TPV. In addition, document D8 points to the fact that "*[i]n many cases, the initial release increases with increasing protein loading*" (page 8, right-hand column, paragraph following the heading "Drug loading"). Thus, review article D8 considers, in addition to microparticle morphology (which includes pore distribution and average pore size), several other strategies for reducing initial burst.

The skilled person could thus have opted for minimising pore-related effects by managing particle morphology.

10.5 The board is of the opinion that starting from the disclosure of closest prior art document D2, the skilled person could have changed the composition of Batch 4 of Example 9 in several ways. In the current case, these various required changes cannot be considered as isolated changes. As can be seen from points 10.1 to 10.4 above, these changes may result in undesired effects. E.g. the increase in exendin-4 content, while leading to better patient compliance (see point 10.1), increases at the same time the initial burst (see point 10.4). Sucrose levels may not be decreased indefinitely while not compromising the stability of the active peptidic agent (see point 10.2). pH related effects influence both polymer matrix integrity and the stability of exendin-4 (see point 10.3). In addition, obtaining a consistently low TPV may depend on the presence or absence of further excipients (see point 8.3 above).

The board considers that the features exendin-4 concentration, sucrose concentration, TPV, and the absence of a buffer and salting-out salts mutually

influence each other, i.e. there is functional reciprocity between these features in achieving an exendin-4 sustained release formulation with a favourable (i.e. reduced) initial burst.

Consequently, the combination of features as defined in claim 1 cannot be considered obvious in view of the teachings in documents D2, D8 or D9, alone or taken in combination.

Consequently, the subject-matter of claim 1 is considered to involve an inventive step.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is maintained as granted.

The Registrar: The Chairwoman:

I. Aperribay M. Pregetter

Decision electronically authenticated