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Datasheet for the decision of 5 October 2023

Case Number: T 1356/21 - 3.3.07

Application Number: 11720115.2

Publication Number: 2571517

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Language of the proceedings: EN

Title of invention:
LONG - ACTING FORMULATIONS OF INSULINS

Patent Proprietor:
SANOFI

Opponent:
Cooke, Richard

Headword:
Long-acting formulations of insulins / SANOFI

Relevant legal provisions:
EPC Art. 54(5), 56
RPBA 2020 Art. 12(4), 12(6), 13(2)

Keyword:
Late-filed evidence - admitted (no)
Novelty - selection invention (yes)
Inventive step - bonus effect (no)

Decisions cited:
G 0002/08, T 0759/08, T 0085/93, T 0261/15, T 1074/06, T 0506/92, T 0192/82, T 0227/89, T 1147/16, T 1317/13, T 0021/81

Catchword:
1. Novelty in the case of purpose-limited product claims pursuant to Article 54(5) EPC relying on a dosage regimen defined by a numerical range, see point 2.6 of the reasons.
2. Limits to the application of the concept of bonus effect, see point 3.4.3 of the reasons.

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Case Number: T 1356/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 5 October 2023

Appellant: (Opponent)	Cooke, Richard Elkington and Fife LLP Patents Department 3-4 Holborn Circus London EC1N 2HA (GB)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
Respondent: (Patent Proprietor)	SANOFI 46 avenue de la Grande Armée 75017 Paris (FR)
Representative:	Zwicker, Jörk ZSP Patentanwälte PartG mbB Hansastraße 32 80686 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 25 June 2021 concerning maintenance of the European Patent No. 2571517 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	A. Jimenez

Summary of Facts and Submissions

I. The appeal was filed by the opponent (appellant) against the interlocutory decision of the opposition division finding that, on the basis of the main request filed during the oral proceedings on 15 April 2021, the patent met the requirements of the EPC.

II. Claims 1, 11 and 23 of the main request pertained respectively to:

Claim 1: "An aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine, wherein the concentration of insulin glargine is 270-330 U/mL being equimolar to 270-330 IU human insulin, and further comprising in the range of 20 - 400 µg/ml zinc."

Claim 11: "An aqueous pharmaceutical formulation with pH between 3.4 and 4.6 comprising insulin glargine for use in the treatment of Type I and Type II Diabetes Mellitus in a patient, wherein the concentration of insulin glargine is 270-330 U/ml being equimolar to 270-330 IU human insulin, and further comprising in the range of 20 - 400 µg/ml zinc."

Claim 23: "The aqueous formulation according to any of the foregoing claims for use in the treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus."

III. The appealed decision cited the following documents:

D1: US 2004/048783 A1
D10: Lantus® FDA label, 2000

D11: Werner et al., poster abstract, 37th Annual Meeting of Endocrine Society of India, Tirupati, A.P. India ESICON, 2007
D12: DE 10 2008 053048 A1
D20: Cochran et al., Diabetes Care 2005, 28(5), 1240-1244
D21: Lane et al., Endocrine Practice, 2009, 15(1), 71-79
D22: Binder et al., Diabetes Care, 1984, 7(2), 188-199
D23: Muchmore et al., J Diabetes Sci Technol, 2010, 4(2), 419-428
D24: Søeborg et al., Eur J Pharm Sci, 2009, 36, 78-90
D27: Joshi et al., 2009, SA Fam Pract, 51(2), 97-102
D28: Gin et al., 2005, Diabetes Metab 31, 7-13
D29: Master's Thesis of Christian Hove Rasmussen on Subcutaneous Insulin Absorption, Part I, 2009

IV. The opposition division decided that:

(a) D12 did not disclose a product having a concentration range of insulin as defined in claim 1. Hence the criteria of novelty were met.

(b) Documents D19-D33 were admitted into the proceedings.

(c) Starting from the closest prior art D11, the subject-matter of claim 1 differed by a higher concentration of insulin glargine and a specific concentration of zinc. The problem to be solved was the provision of an improved insulin glargine formulation, showing a flatter PK profile and prolonged activity. The claimed solution involved an inventive step. The findings in the prior art regarding the concentration dependency of the PK-

profile of NPH or regular insulin could not be extrapolated to insulin glargine.

V. The opponent (appellant) lodged an appeal against the opposition division's decision. With their statement setting out the grounds of appeal, the appellant filed the following documents:

A34: Chapter 9 "Parenteral Dosage Forms' by Broadhead and Gibson of "Pharmaceutical Preformulation and Formulation - A Practical Guide from Candidate Drug Selection to Commercial Dosage Form", Informa Healthcare USA, Inc., 2009
A35: Expert declaration by M.A. Weiss
accompanied by Exhibits 1-24

VI. With their reply dated 21 March 2022, the patent proprietor (respondent) submitted the following documents:

A36: Expert declaration by Prof. Kirsch
accompanied by Exhibits 1-35
A37: Abstract 2349-PO
A38: Humalog Assessment

VII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VIII. Oral proceedings were held before the Board on 5 October 2023.

IX. The appellant's arguments may be summarized as follows:

(a) A34 and A35 (together with the 24 accompanying exhibits) were filed as evidence of common general knowledge and in direct reaction to the opposition

division's decision on inventive step. Accordingly, these documents were to be admitted into the appeal proceedings.

(b) The subject-matter of claims 11-23 lacked novelty over D12. The claimed insulin glargine concentration of 270-330 U/mL fell within the broad meaning of the term "dosage regimen" as used in G 2/08, but did not provide a particular technical effect as compared with the range 100-500 U/mL known from D12, and therefore could not establish novelty.

(c) Regarding inventive step, starting from any of D1 or D10-D12, the formulation of claim 1 of the main request differed by the insulin glargine concentration of 270-330 U/mL. The technical effects of using a concentration of 300 U/mL instead of 100 U/mL were:
(a) a reduced volume of injection, and
(b) a flatter PK/PD profile with a longer duration of action.
The objective technical problem was the provision of an improved aqueous pharmaceutical formulation of insulin glargine. Increasing the insulin glargine concentration to reduce injection volume was obvious. The PK/PD effects merely represented bonus effects, and could not provide a basis for inventive step. In any case, increasing the insulin glargine concentration for a flatter PK/PD profile with a prolonged duration of action was also obvious. The claimed subject-matter was accordingly not inventive.

X. The respondent's arguments may be summarized as follows:

(a) Declaration A35 and its 24 annexes, as well as A34, were an amendment to the appellant's case and were not to be admitted. These numerous documents could and should have been filed before and were not *prima facie* relevant.

(b) Claims 11-23 of the main request did not specify a dosage regimen, but a concentration of the formulation, such that G 2/08 was not applicable. Even if it was applicable, G 2/08 established that novelty of a dosage regimen selected from a broader range was determined by the same criteria as any other selection invention from a broader range, which criteria did not include the requirement of a purposive selection anymore. The claimed subject-matter was thus novel over D12.

(c) Starting from any of D1 or D10-D12, the distinguishing feature was the concentration of insulin glargine in the range of 270-330 U/mL. The objective technical problem was the provision of an aqueous pharmaceutical formulation of insulin glargine with a flatter exposure and a flatter biological profile. The improvement of PK/PD properties of insulin glargine had a greater practical importance for a basal insulin formulation than the reduction of injection volume, and there was no "one-way street situation" such that the PK/PD technical effect was not a mere bonus. The claimed solution involved an inventive step.

XI. The appellant requests that the decision under appeal be set aside and that the patent be revoked in its

entirety. The appellant further requests that A36-A38 not be admitted into the proceedings.

XII. The respondent requests that the appeal be dismissed and that the patent be maintained on the basis of the main request upheld by the opposition division, or, alternatively, that the patent be maintained on the basis of one of auxiliary requests 1-8 as filed with the reply to the appeal on 21 March 2022.

The respondent further requests that neither D29, nor A34 or A35 and its 24 exhibits be admitted into the appeal proceedings. The respondent also requests that the appellant's argument of lack of inventive starting from D10 not be admitted into the appeal proceedings.

Reasons for the Decision

1. Procedural matters

1.1 Admittance of D29

The Board found that document D29, a Master's Thesis filed before and admitted by the opposition division, was not only part of the appeal proceedings but also available to the public. No reasoning in this respect is necessary here, considering the Board's conclusion (see below) that the appellant's main request meets the requirements of novelty and inventive step even taking D29 into account.

1.2 Admission of A34-A38 and the accompanying exhibits

1.2.1 Together with the statement setting out the grounds of appeal, the appellant filed document A34, declaration A35 and 24 accompanying documents (exhibits). With their reply to the appeal, the respondent filed declaration A36, its 35 accompanying exhibits, and documents A37 and A38. The parties debated the admittance of these documents.

The provisions of Articles 12(4) and (6) RPBA 2020 are applicable. A34-A35 and A36-A38 are regarded as amendments to the appellant's and respondent's cases, respectively, and may be admitted only at the discretion of the Board. Under Article 12(4) RPBA 2020, the Board shall exercise its discretion in view of, *inter alia*, the complexity of the amendment, the suitability of the amendment to address the issues which led to the decision under appeal, and the need for procedural economy. Furthermore, under Article 12(6) RPBA, the Board shall not admit evidence which should have been submitted in the first instance proceedings, unless the circumstances of the appeal case justify their admittance.

1.2.2 In the case of A34, A35 and its 24 exhibits, the sheer number of documents filed, and the resulting complexity of the amendment to the appellant's case, run counter to the principle of procedural economy. These documents may not be admitted into the appeal proceedings for this reason already.

1.2.3 Additionally, the Board shares the respondent's opinion that these documents should have been filed in the first instance proceedings, considering the following circumstances:

In their notice of opposition dated 24 December 2018, the appellant had based their case on 12 documents. With their later submission of 14 December 2020, the appellant filed 22 new documents (namely D19-D33 and accompanying exhibits) and introduced for the first time objections and considerations relating to bonus effect or combination with documents pertaining to regular insulin or NPH. The opposition division admitted these new submissions, but nonetheless found that the main request met the requirements of inventive step.

Under these circumstances, the filing of 26 new documents with the statement of grounds of appeal cannot be regarded as a legitimate reaction to the inventive step reasoning in the appealed decision. The fact that the reasons given in the appealed decision on the issues of bonus effect and regular insulin or NPH were not hinted at in the opposition division's preliminary opinion (dated 3 September 2019, i.e. before the filing of D19-D33) is precisely due to the appellant's procedural behavior. The appellant cannot base their plea for admittance of A34 and A35 on their own failure to file D19-D33 in good time in the first instance proceedings. In any case, the matters of bonus effect and regular insulin or NPH had already been addressed by the respondent during the opposition proceedings (see the written submission filed on 15 February 2021, point 3 regarding the admissibility of documents D19-D32 and point 5.3.6 discussing the "bonus effect"). Regardless of the opposition division's opinion, any additional documents relating to these issues should have been submitted during the first-instance proceedings.

1.2.4 This conclusion is not modified by the fact that some of the documents filed with the statement of grounds of appeal (such as A34) may be evidence of the skilled person's common general knowledge. The appellant emphasized that, according to T 759/08 (see point 2.2 of the reasons), common general knowledge can in principle not be viewed as complicated or surprising subject-matter, because it is well known to those skilled in the art. However, as explained in T 85/93 (point 1.1 of the reasons), evidence of common general knowledge, like any other evidence in support of an opponent's submissions, should be filed at an early stage in the proceedings before the opposition division, and might be rejected as inadmissible at the board's discretion if filed for the first time during appeal proceedings. This principle holds good under the currently valid Rules of Procedure of the Boards of Appeal (RPBA 2020). Here, the Board considers that documents A34 and A35, together with the 24 exhibits, including the documents reflecting common general knowledge, should have been filed during the proceedings before the opposition division, and that the circumstances of the appeal case do not justify their admittance.

1.2.5 In their letter dated 2 October 2023, the appellant auxiliarily requested that at least exhibits 4, 11 and 21-23 of A35 be admitted, and merely stated that the reasons for compliance of these exhibits with the requirements of Article 12(4) RPBA would be explained in detail at the oral proceedings.

Thus, until the filing of the above letter only three days in advance of the oral proceedings before the Board, the appellant had given no indication that exhibits 4, 11 and 21-23 of A35 would be of any more

significance than the numerous other exhibits, let alone than the declaration A35 itself. Additionally, the appellant left the explanations of any such significance for the day of the oral proceedings.

The Board decided not to admit exhibits 4, 11 and 21-23 either, firstly because this subset of late filed documents should have been filed before the opposition division just as the other documents filed with the grounds of appeal, and secondly because providing additional reasons for the admittance of exhibits 4, 11 and 21-23 at the latest stage of the appeal proceedings represents a further amendment to the appellant's case, which is to be rejected under Article 13(2) RPBA 2020 for lack of any exceptional circumstances.

1.2.6 Accordingly, the Board did not admit any of A34, A35 and the accompanying exhibits.

1.2.7 The admittance of documents A36, its exhibits, and A37-A38, was contested by the appellant, and was requested by the respondent only in case the Board would admit documents A34, A35 or its exhibits. Accordingly, the Board did not admit either any of A36-A38, including the accompanying exhibits.

2. Main request, novelty over D12

2.1 Claim 1 of the main request pertains to an aqueous pharmaceutical formulation characterised in particular in that "the concentration of insulin glargine is 270-330 U/mL being equimolar to 270-330 IU human insulin". This feature of claim 1 defines the concentration of insulin glargine in the composition, expressed as (international) units (U or IU) (see the patent, paragraph [0005]).

Claim 11 is identical to claim 1 with the addition of "for use in the treatment of Type I and Type II Diabetes Mellitus in a patient". Claim 23, pertaining to the "aqueous formulation according to any of the foregoing claims for use in the treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus", relates to the same subject-matter as claim 11. Thus both claims 11 and 23 are drafted in the format of Article 54(5) EPC, i.e. as claims directed to the same composition as in claim 1 for a specific use in a method referred to in Article 53(c) EPC.

2.2 According to the appellant, the subject-matter of claims 11-23 of the main request lacks novelty over D12, because the insulin glargine concentration defined in said claims falls within the broad meaning of the term "dosage regimen" as used in G 2/08, and yet is not characterised by any technical effect that would be particular to said sub-range compared to other concentrations within the range disclosed in D12. The appellant did not, however, object to the novelty of claim 1.

2.3 D12 describes compositions comprising an insulin such as insulin glargine (i.e. "Gly(A21)-Arg(B31)-Arg(B32)-Humaninsulin") having most preferably a pH of 4.0-4.5 (see paragraph [0092] of D12) and optionally zinc in a preferred range of 5-200 µg/ml (see paragraph [0087]). D12 also generally mentions a preferred insulin concentration range of 40-500 U/ml (see paragraph [0080]).

2.4 It is undebated that D12 does not disclose a concentration of insulin glargine in the composition in the claimed range of 270-330 U/ml. The opposition

division's finding that this claimed range is narrow compared to the range of D12 (criterion (a)) and far removed (criterion (b)) from any specific example of this document, in which the concentration of insulin glargine is always 100 U/ml, is also not contested (see §4.2.1 of the appealed decision). In this respect, the Board concurs with the most recent decisions, including T 261/15 (see point 2.2.2 of the reasons), according to which the former criterion of purposive selection (criterion (c)) is relevant for the question of inventive step rather than for novelty (see also Case Law of the Boards of Appeal, 10th edition, 2022, I.C. 6.3.1). This is reflected in the Guidelines for Examination in the EPO, which state since 2019 that only criteria (a) and (b) need to be fulfilled (see G-VI, 8 (ii) - November 2019 version). For the sake of completeness in relation to this point, the Board observes that already in the landmark decision T 198/84 it was affirmed that the presence of a newly discovered effect in a sub-range singled out of a larger range (purposive selection) was not a prerequisite for novelty (see point 7). Thus the subject-matter of claim 1 is novel over D12.

2.5 As to claims 11 and 23, the fact that the compositions of these claims are limited, in comparison with claim 1, by the feature pertaining to their specific use in a method of treatment of Type I or II Diabetes Mellitus, does not entail that the features pertaining to the concentration of insulin glargine should not longer be regarded as defining the composition, but merely its use. Neither decision G 2/08 (see points 6.1 and 6.3, which merely abstain from precisely defining the term "dosage regimen") nor its reference to T 1074/06 (where the claims related to doses, and not concentration) justify reading the word "concentration" of claims 11

and 23 as a dosage regimen. In claims 11 and 23 just as in claim 1, the concentration feature defines the composition itself, i.e. the amount of insulin glargine in the composition, and not the use of the composition, i.e. the dose given to a patient at particular times or time intervals. This concentration feature thus establishes novelty for the subject-matter of claims 11 and 23 for the same reasons as for claim 1.

2.6 Additionally, considering the case law in the general situation of selections from numerical ranges (see 2.4 above), the Board is not convinced by the appellant's argument that in the case of purpose-limited product claims pursuant to Article 54(5) EPC relying on a dosage regimen defined by a numerical range, a selection from the prior art must be purposive for it to be novel.

In point 6.3 of G 2/08 the Enlarged Board of Appeal stated that "the claimed definition of the dosage regime must therefore not only be verbally different from what was described in the state of the art but also reflect a different technical teaching". However, under the same point of the reasons the Enlarged Board of Appeal explained that "for the assessment of novelty and inventive step of a claim in which the only novel feature would be the dosage regimen, the whole body of jurisprudence relating to the assessment of novelty and inventive step generally also applies". In the Board's view, this indicates that G 2/08 did not seek to establish different novelty criteria for numerical ranges in the case of dosage regimen. Thus, the case law in the general situation of numerical ranges, as it has evolved over the years, must apply also in the case of dosage regimen. Consequently, the appellant's objection must fail for the additional reason that,

even if the concentration features of claims 11 and 23 were *arguendo* seen as a dosage regimen, the former criterion of a purposive selection (criterion (c)) should no longer be regarded as a requirement under G 2/08 for a dosage regimen to represent a novel selection from a broader range known in the prior art.

2.7 Accordingly, the claimed subject-matter is novel.

3. Main request, inventive step

3.1 The present invention relates to insulin glargine formulations. As explained in the patent (see paragraphs [0002] and [0004]), insulin glargine is an analogue of human (regular) insulin. The known Lantus® formulation of insulin glargine was developed to meet the medical need for a long-acting insulin product that can be administered as a single daily injection to yield normal or near-normal blood glucose control with a basal insulin profile that is as smooth as possible over a 24-hour period.

3.2 Closest prior art and differentiating feature

Among documents D11, D1 and D12, the opposition division selected D11 as the closest prior art. In appeal, the appellant raised objections of lack of inventive step starting from D11, D1 and D12, and additionally considered D10 as an alternative suitable starting point.

In the case at hand, the choice of the starting document has no bearing on the assessment of inventive step, because the embodiment chosen as starting point is in all cases a 100 U/mL glargine composition (see D1, examples; D10, Lantus composition, page 1; D11,

U-100 insulin glargine; D12, Lantus composition) and the relevant differentiating feature is the claimed insulin glargine concentration of 270-330 U/mL. It is consequently not necessary to identify precisely the document(s) used as starting point(s), or to decide whether the objection based on D10 should be admitted into the appeal proceedings.

3.3 Technical effects

The differentiating feature, namely the increase in insulin glargine concentration from 100 U/mL to 270-330 U/mL, leads to two types of technical effects:

Effect 1: reduced discomfort or pain

According to the patent (see paragraph [0005]), "A considerable number of patients, in particular those with increased insulin resistance due to obesity, use large doses to control blood glucose. For example, a dose of 100 U requires injection of 1 ml Lantus® U100, which may confer some discomfort [...]. To reduce the volume of injection, a formulation containing 300 U insulin glargine per ml has been developed. [...] This formulation would allow patients to inject the same number of units of insulin glargine at one third the volume of injection." In this respect, the Board concurs with the respondent that the effect is a reduced discomfort upon injection, and not a reduced volume of injection, this latter aspect being instead the means leading to the effect.

Effect 2: flatter PK/PD profile, longer duration of action

The patent further indicates that insulin glargine U 300 is not equivalent to insulin glargine U 100 in bio-availability (exposure, referred here as PK - pharmacokinetic) and bio-efficacy (i.e. activity, referred here as PD - pharmacodynamic) (see paragraphs [0017] and [0018]). As concluded by the opposition division (see §5.3 of the appealed decision), figures 1-3 of the patent demonstrate that insulin glargine U 300 exhibits flatter PK and PD profiles and longer duration of action than insulin glargine U100.

The appellant does not contest that both effects 1 and 2 are achieved by the composition with a concentration of 300 U/mL in comparison with the prior art embodiment having a concentration of 100 U/mL. The appellant however submits that the effects are not specific to the claimed range of 270-330 U/mL, but also arise with other concentrations falling within the broader range disclosed in D12 for insulins in general, such as 500 U/mL. The Board does not consider that this argument modifies the assessment of the technical effect over the closest prior art. The starting point for the evaluation of inventive step is the 100 U/mL insulin glargine composition, and not a hypothetical 500 U/mL insulin glargine composition which would conceptually fall within the scope of D12. Accordingly, it is enough that the effects arise in comparison with the 100 U/mL composition, and it is not required that these effects exclusively arise in the claimed range of 270-330 U/mL, for them to be acknowledged and taken into account.

3.4 Technical problem; bonus effect

The parties differ as to which of the two effects should be taken into account in the assessment of inventive step.

3.4.1 In the Board's view, both effects are mentioned in the patent (see paragraph [0005] for the reduced discomfort, and paragraphs [0017] and [0018] for the flatter PK/PD profile with a longer duration of action) and are credibly achieved by the claimed subject-matter in comparison with the closest prior art embodiment. Accordingly, the technical problem is to be formulated objectively, taking into account both effects, as the provision of an improved aqueous pharmaceutical formulation of insulin glargine, i.e. the improvement being both a flatter exposure and flatter biological profile together with a longer duration of action, and a reduced discomfort.

3.4.2 According to the appellant, the reduction in the injection volume is the relevant effect, and was, as acknowledged in the patent, the purpose for increasing insulin glargine concentration in the first place. The additional effect of the concentration-dependent change of the PK/PD profile would be inevitably achieved as the result of increasing the insulin glargine concentration for the purpose of reducing the injection volume, and would thus represent a mere bonus effect.

The Board does not agree, for the following reasons.

3.4.3 According to established case law, an effect which may be said to be unexpected can be regarded as an indication of inventive step. However, certain preconditions have to be met (see Case Law of the Boards of Appeal, 10th edition, 2022, I.D.10.8). In T 21/81 (see Headnote) the board considered that "if

having regard to the state of the art it would already have been obvious for a person skilled in the art to arrive at something falling within the terms of a claim, because an advantageous effect could be expected to result from the combination of the teachings of the prior art documents, such claim lacks inventive step, irrespective of the circumstance that an extra effect (possibly unforeseen) is obtained." In line with this decision, in T 506/92 it was affirmed that an additional effect achieved inevitably by the skilled person on the basis of an obvious measure without any effort on his part simply represents a bonus under EPO case law which cannot substantiate inventive step, even as a surprising effect (see point 2.6 of the reasons).

However, in the Board's view, the case law on bonus effects cannot be applied to all situations where a given differentiating feature (here: the increase in insulin glargine concentration) leads to (or inevitably achieves) two separable technical effects (here: reduced discomfort/injection volume; and flatter PK/PD profile/longer duration of action), one of which may be expected. For an additional, unexpected effect to be disqualified as a mere bonus effect, it must be shown either that the situation is characterised by a lack of alternatives as regards the means for achieving the first, expected improvement (i.e. a "one-way-street" situation as explained in T 192/82), or that, considering the relative technical and practical importance of the effects in the circumstances of the case, the additional unexpected effect is merely accidental (following T 227/89 and T 1147/16). In situations which do not qualify as a "one-way street", the Board does not consider it appropriate that a crucial and unexpected technical advantage be disregarded in the assessment of inventive step as soon

as any additional obvious effect is mentioned in the patent.

The Board is aware of the view expressed in T 1317/13 (see point 24 of the reasons) that a "one-way-street" situation is not a mandatory prerequisite for the application of the principle established in T 21/81 (see above). However, neither T 1317/13 nor T 21/81 offer a basis for an unqualified application of the bonus effect case law to any situation of plurality of technical effects without regard to their respective technical and practical importance. The Board's view in this regard is in agreement with the statement in decision T 192/82 (see point 16 of the reasons) that the use of means leading to some expected improvements might well be patentable if relying on an additional effect, provided this involves a choice from a multiplicity of possibilities.

3.4.4 The present case does not qualify as a "one-way-street" situation. As argued by the respondent, the skilled person could have addressed the issue of discomfort caused by the injection of larger volumes of the formulation by other means than an increased concentration, such as dividing the injection into several smaller volumes, adding further substances that facilitates diffusion at the injection site avoiding the formation of a large depot, heating the injection site to increase diffusion, including an analgesic, reducing the speed of injection, using continuous injection or adjusting the depth of injection. D20 (see page 1240; page 1242, right column) and D21 (see page 71, Results) merely express a preference, in the context of regular insulin, for the use of a (concentrated) U-500 formulation with multiple daily injections or continuous subcutaneous (s.c.) infusion.

It cannot be concluded from these documents that the present case is characterised by a lack of alternative means for addressing the issue of discomfort associated with the injection of large volumes.

3.4.5 Furthermore, the effects of flatter PK/PD profiles and longer duration of action cannot be regarded as merely accidental, but instead represent crucial advantages in the context of basal insulins. As explained in D27 (see page 98, section "Basal Insulin"), basal insulins are meant to provide a constant background level of insulin that controls hepatic plasma glucose production on a diurnal basis. Basal insulins include insulin glargine and NPH insulin. The ideal properties for a basal insulin are the following:

"Its action should be protracted to ensure glycaemic control over long time periods with few injections (i.e. have a long duration of action). The kinetic profile should be flat and smooth (i.e. peakless) with minimal variability between patients and within each patient from day to day to ensure predictability of control and to lower the risk of hypoglycaemia."

The effects of flatter PK/PD profiles and longer duration of action thus correspond to essential properties of basal insulins. These effects cannot be regarded as being technically and practically less important that the reduced discomfort upon injection.

3.4.6 Lastly, the patent explains in paragraphs [0005] and [0006] that the formulation containing 300 U/mL insulin glargine was initially developed for the purpose of reducing the injection volume, and thus to address the issue of discomfort upon injection of larger doses of the U 100 formulation in patients e.g. with increased

insulin resistance. The inventors expected both the U 100 and U 300 formulations to provide the same insulin exposure and effectiveness, yet unexpectedly discovered that the U 300 formulation instead led to flatter PK/PD profiles (see paragraph [0017]).

According to the appellant, this PK/PD effect was discovered only after arriving at the higher concentration formulation, and would thus be nothing but an additional bonus effect. However, in the Board's opinion, it would also not be appropriate to disqualify the effect of flatter PK/PD profiles and longer duration of action as accidental, i.e. as being of lesser technical and practical importance, on account that these effects may be the result of a serendipitous discovery. What matters when deciding if the pK/PD profile effect is to be taken into account is not in what circumstances the inventors realised the invention, but what the invention achieves.

3.4.7 Thus, in the circumstances of the present case where several alternatives could lead to reduced discomfort upon injection, and owing to their crucial importance, the technical effects of flatter PK/PD profiles and longer duration of action cannot be regarded as accidental and must be taken into account.

Similarly, the Board is not convinced that the effect of reduced discomfort and injection volume should be regarded as a bonus effect either. For the reasons given above (see 3.4.3), the fact that two technical effects arise from the same distinguishing feature does not mean that one of the two effects must necessarily be regarded as a bonus effect. However, considering that the effect on PK/PD profile and duration of action must be taken into account and already leads to the

acknowledgement of an inventive step (see below), the question whether the reduced discomfort and injection volume should be additionally considered may be left unanswered.

3.5 Obviousness

It follows from the above that the relevant question is whether the skilled person not only could, but would consider an increase of the insulin glargine concentration to 270-330 U/mL in the expectation of solving the problem, and in particular in the expectation of achieving a flatter PK/PD profile and longer duration of action.

The prior art is silent about the effect of a higher concentration on the PK and PD profiles in the context of insulin glargine. Contrary to the appellant's view, the Board does not consider that the prior art relating to regular insulin and insulin NPH would allow the skilled person to anticipate this effect for insulin glargine either.

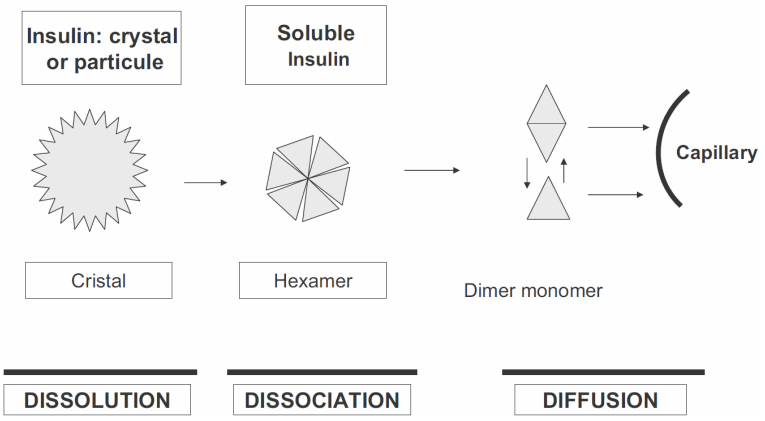
D20-D23 teach that the absorption rate of s.c. injected regular insulin is decreased, and its duration of action is extended, when raising the concentration of regular insulin in the formulation from 100 U/mL to 500 U/mL (see D20, page 1241, middle column; D21, page 72, right column; D22, abstract; D23, page 423, right column). While the person skilled in the field of insulins would be aware of the content of D20-D23, there is no reason why they should generalise this teaching to the different derivative insulin glargine.

D24 and D29 relate to a mathematical model for predicting the concentration dependent absorption

kinetics of Neutral Protamine Hagedorn (NPH) insulin, which is regular soluble insulin formulated with protamine. The simulations disclosed in D24 and D29 suggest a flatter and prolonged plasma insulin curve if the concentration of a NPH insulin formulation is increased above U 100 (see e.g. figures 11(a) and (b) of D24). It is debatable whether these simulations represent a credible teaching regarding the real-life impact of concentration on PK/PD profile for NPH insulin, considering the high degree of variation of the model depending on the choice of the variables α and β (see figure 10, page 85 of D24; D29, §4.1-4.3) and the strong reservations expressed in D29 (see §4.7). But in any case, there is also no basis for extrapolating these teachings regarding NPH insulin, if any, to insulin glargine. The teaching that an increased concentration leads to a flatter PK/PD profile and longer duration of action in the particular cases of regular insulin and, possibly, NPH insulin, is not enough for the skilled person to anticipate that the same modification would have the same effect in the case of insulin glargine. Such a generalisation is based on hindsight.

The appellant further relied on alleged similarities between the mechanisms for absorption of NPH insulin and insulin glargine. This line of argumentation is also not convincing. It is not contested that both insulin glargine and NPH form a solid depot after s.c. injection. However, the analogy must stop there. As disclosed in D28 (see the paragraph bridging pages 8 and 9; see also figure 1, reproduced below), NPH insulin is known to be presented as a crystalline suspension. Once injected in the subcutaneous tissue, the crystalline structure must be destructured in order to release the insulin complexes followed by the

hexamers, which, in turn, dissociate into dimers and monomers.



In contrast, in the case of insulin glargine, D28 indicates that "injection into subcutaneous tissue produces an homogenous and diffuse precipitate which subsequently releases its monomers" (see page 9, right column). The nature of this precipitate is unknown. There is no hint in D28 that insulin glargine produces crystalline hexamers in this depot or has to go through the same steps as NPH insulin to be absorbed. The appellant's assumption that the absorption of s.c. injected insulin glargine and NPH from the depot into the patient’s circulation would be governed by the same basic processes is thus not supported by the evidence presented.

As a consequence, the skilled person had no reasonable expectation that raising the concentration of insulin glargine from 100 U/mL to 270-330 U/mL would lead to flatter PK/PD profiles and a longer duration of action.

Accordingly, the subject-matter of the main request involves an inventive step.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated