Deckblatt Übersetzung

Daten der Übersetzung:

Court/Gericht:	Bundesgerichtshof
Date of Decision / Datum der Entscheidung:	2015-01-13
Docket Number / Aktenzeichen:	X ZR 41/13
Name of Decision / Name der Entscheidung:	Quetiapin

FEDERAL COURT OF JUSTICE

IN THE NAME OF THE PEOPLE

JUDGMENT

X ZR 41/13

Pronounced on:
13 January 2015
Bürk
Judicial Secretary as
Clerk of the court
registry

in the patent nullity proceedings

Quetiapin

EPC Art. 52(1); Patent Act Sec. 1(1)

When defining the technical problem underlying an invention, it must not be assumed without further ado that it was appropriate for the skilled person to deal with a specific problem. Rather, the technical problem must be formulated in such a general and neutral manner that the question of what suggestions the skilled person received from the state of the art in this respect arises exclusively when examining the inventive step.

Federal Court of Justice, judgment of 13 January 2015 - X ZR 41/13 –
Federal Patent Court

The X. Civil Senate of the Federal Court of Justice, following the oral hearing on 13 January 2015, attended by the presiding judge Prof. Dr. Meier-Beck, the judges Gröning, Dr. Bacher and Dr. Deichfuß as well as the judge Dr. Kober-Dehm

ruled that:

The appeal against the judgment of the 3rd Senate (Cancellation Senate) of the Federal Patent Court pronounced on 13 November 2012, is dismissed at the defendant's expense.

By operation of law

Facts of the case:

1 The defendant is the proprietor of European patent 907 364 (the patent in suit), which was granted with effect for the Federal Republic of Germany, was filed on 27 May 1997, claiming a priority of 31 May 1996, and relates to a medicament consisting of a sustained-release dibenzothiazepine derivative. Claim 1, to which nineteen other claims are referred back, reads in the language of the proceeding:

> "A sustained release formulation comprising a gelling agent and 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable excipients."

2 The plaintiffs have argued that the subject matter of the patent in suit is not patentable. The first plaintiff also claimed that the invention was not disclosed in the patent in suit in such a way that the skilled person could carry it out. The defendant defended the patent in suit as granted and, in the alternative, in four amended versions.

3 The Patent Court declared the patent in suit null and void. The defendant challenges this with its appeal, in which it continues to pursue its first-instance claims. The plaintiffs oppose the appeal.

Grounds of the decision:

4 The admissible appeal is unfounded.

5 I. The patent in suit concerns a retard formulation with the active ingredient quetiapine.

6 1. According to the statements in the patent specification, it was known in the state of the art that the active ingredient 11-[4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo-[b,f][1,4]thiazepine (non-proprietary name: quetiapine) has antidopaminergic activity and can be used, for example, as an antipsychotic or for the treatment of hyperactivity.

7 The patent in suit further states that in the treatment of a number of diseases, it is desirable to provide the active pharmaceutical ingredients in sustained release form to ensure a uniform and constant rate of release over an extended period of time without frequent administration. In the state of the art, numerous sustained-release formulations containing gelling agents such as hydroxypropylmethylcelluloses were known. However, the preparation of such formulations of soluble drugs had proved difficult. Water-soluble drugs tend to exhibit a phenomenon known as dose dumping, in which release is initially delayed but then begins at a high rate. There is also a tendency for fluctuations and diurnal variations in plasma concentration. Finally, it is difficult to control the rate of release. Therefore, there is a need for sustained-release formulations of soluble drugs such as quetiapine that can overcome or reduce these difficulties.

8 2. The Patent Court inferred from this that the patent in suit concerned the technical problem of providing a formulation of the active ingredient quetiapine that would allow the release rate to be as constant as possible over as long a period of time as possible.

9 3. This definition is too narrow. Rather, the problem underlying the patent in suit is to provide a dosage form of quetiapine that results in an improved effect.

10 a) The definition used by the Patent Court is indeed suggested by the wording of the description. However, as the Patent Court did not misjudge in its

approach and as the parties also agree in their approach, this is not necessarily of decisive importance.

11 According to the case law of the Senate, the starting point for the examination for inventive step is not necessarily the "task" to be taken from the description of the patent in suit (Federal Court of Justice, judgment of 1 March 2011 - X ZR 72/08, GRUR 2011, 607 marginal no. 19 - Kosmetisches Sonnenschutzmittel III). Rather, the decisive factor is what the invention actually achieves as compared to the state of the art (see only Federal Court of Justice, judgment of 12 February 2003 - X ZR 200/99, GRUR 2003, 693, 695 - Hochdruckreiniger).

12 b) However, contrary to the opinion of the appeal, it does not follow from this that all advantages which the invention objectively entails must be taken into account cumulatively when defining the technical problem.

13 According to the case law of the Senate, an invention may concern several different technical problems. In such constellations, the individual problems must be considered separately when examining patentability. Patentability may already have to be denied if overcoming one of these problems was part of the scope of the skilled person and the claimed invention was suggested by the state of the art from this starting point (Federal Court of Justice, judgment of 1 March 2011 - X ZR 72/08, GRUR 2011, 607 marginal no. 19 - Kosmetisches Sonnenschutzmittel III).

14 Against this background, the question disputed between the parties as to whether the formulation claimed by the patent in suit not only enables a constant release rate over a long period of time but also opens up additional fields of application and indications for quetiapine is not relevant for the decision of the dispute. Insofar as the skilled person had reason to search for a formulation with a constant release rate and the subject matter of the patent in suit was suggested by the state of the art on the basis of this problem, patentability must be denied even if the invention is suitable for solving further problems in addition.

15 c) However, the definition of the technical problem used by the

Patent Court is too narrow because the dispute raises, inter alia, the question of whether the skilled person had reason to consider a formulation for quetiapine that allows a release rate that is as constant as possible over as long a period as possible.

16 The definition of the technical problem underlying an invention does not serve to make a preliminary decision on the question of patentability. Therefore, elements which are part of the patentable solution may not be taken into account (Federal Court of Justice, judgment of 22 May 1990 - X ZR 124/88, GRUR 1991, 811, 814 - Falzmaschine; judgment of 30 July 2009 - Xa ZR 22/06, GRUR 2010, 44 marginal no. 14 - Dreinahtschlauchfolienbeutel).

17 For the same reason, it is not permissible to assume without further ado that the skilled person was advised to deal with a specific task. In many cases, it may be clear from the description of the patent or from other circumstances which problems the skilled person would have addressed on the basis of the state of the art. However, if this cannot be assessed beyond doubt, it would be wrong to examine the question of which suggestions were given to the skilled person by the state of the art already when defining the task. Rather, the technical problem must be formulated in such a general and neutral manner that this question arises exclusively in the context in which it is relevant, namely in the examination of the inventive step.

18 d) In the case in dispute, therefore, the technical problem is to provide a dosage form of quetiapine which leads to an improved effect. In contrast, the question of which measures were suggested to the skilled person to achieve this goal is exclusively relevant for the assessment of the inventive step.

19 To solve this problem, the patent in suit proposes a retard formulation containing a gelling agent, quetiapine or a pharmaceutically acceptable salt thereof, and one or more pharmaceutically acceptable excipients.

20 II. The Patent Court concluded that the subject matter of the patent in suit was not based on inventive step, and essentially reasoned as follows:

21 From the publication by Gefvert et al. (Time course for dopamine and

serotonin receptor occupancy in the brain of schizophrenic patients following dosing with 150 mg SeroquelTM tld, European Neuropsychopharmacology, 1995, pp. 347, P-4-65, NiK9 = TM8), the skilled person, a team consisting of a pharmacist with a doctorate in pharmaceutical technology and a medical doctor, found that after administration of the quetiapine immediate-release drug Seroquel, two of three values important for efficacy dropped significantly within 26 hours. This indicated that this drug had to be administered more than once a day to achieve the desired effect. In NiK9, a frequency of administration of once or twice per day was indeed described as desirable. However, the authors' subsequent approach showed that they had not considered the known immediate-release oral dosage form of quetiapine for administration only once per day. A suggestion to consider a formulation with a different release profile to achieve this goal had come from the press release submitted as TM17, which reported that the defendant had commissioned the development of a formulation that would require Seroquel to be administered only once per day.

22 For the skilled person, the use of a gelling agent had also been obvious. It was known from US patent specification 4 389 393 (NiK12) that matrix systems based on gelling agents such as hydroxypropylmethylcelluloses were suitable for formulating a variety of active ingredients.

23 The European patent application 240 228 (NiK3) did not give rise to a different assessment. The latter contained only general dosage information. Further information can only be found in NiK9, which teaches the skilled person to administer a dosage form that releases the active ingredient immediately at least twice a day. The amount of active ingredient presented as beneficial in NiK9 was not so great as to have prevented the skilled person from considering sustained-release formulations. From the publications of Farde et. al (Positron emission tomographic analysis of central D1 and D2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine, Arch. Gen Psychiatry 49 (1992), 538, NiK29), Wetzel et al (Seroquel (ICI 204 636), a putative "atypical" antipsychotic, in schizophrenia with positive symptomatology: results of an open clinical trial and changes of neuroendocrinological and EEG parameters, Psychopharmacology 119 (1995), 231, NiK30), and Gelder et al. (Oxford Textbook of Psychiatry, Third Edition, 1996, ch. 9 p. 246 ff. and ch. 17,

p. 532 ff, NiK32) did not result in a different assessment.

24 The versions of the patent in suit defended by the auxiliary requests differed from the granted version only by additional information on the method of administration (tablet form), the proportion of gelling agent (5 to 50% by weight) and the selection of the gelling agent. All these measures were within the bounds of what is customary from a professional point of view.

25 III. This assessment stands up to scrutiny in the appeal proceedings.

26 1. The appeal complains that the Patent Court wrongly assumed that the pharmaceutical technologist belonging to the team to be regarded as skilled person had several years of experience in the development and production of controlled release formulations. It claims that, within the team, the medical scientist is the driving force who specifies the problems to be overcome.

27 This complaint is not capable of calling the contested judgment into question.

28 It can be assumed in favor of the defendant that within the team consisting of a physician and a pharmacist, the former has the lead and that the pharmacist is not necessarily specialized in retard formulations. However, even such a team is able to access special expertise with regard to such formulations, provided that it recognizes that a controlled release of the active ingredient as a solvent can be considered.

29 2. The Patent Court correctly decided that the subject matter of the patent in suit is not based on inventive step.

30 a) The Patent Court correctly concluded that the skilled person had reason to search for forms of administration by which quetiapine is administered only once a day.

31 aa) A sufficient suggestion for this arose, as the Patent Court correctly found, from the publication by Gefvert et al. (NiK9).

32 In the introduction of NiK9 it is stated that the quetiapine-containing drug Seroquel had been administered three or four times a day in phase II and III

tests. In view of the great importance of reliable intake in schizophrenia patients, a more convenient dosing schedule would be helpful. In the concluding remarks, the hope was expressed that administration once or twice a day might be sufficient.

33 This resulted not only in the suggestion to reduce the number of daily administrations to two, but in any case also in the suggestion to aim for an administration frequency of only once per day.

34 bb) The assessment expressed by the defendant with reference to the statements of its private expert Prof. Dr. M. that administration once a day has no significant advantages over administration twice a day (HE12 p. 8) does not lead to a different assessment in this respect.

35 The above assessment does not call into question the fact that less effort is required both for the patient and for any person entrusted with care or monitoring if the drug only has to be taken once a day. This alone gave reason to consider such a form of administration as an alternative, even if the associated advantages were considered by some experts to be rather minor.

36 That a reduction in the frequency of administration from twice to once per day was not generally regarded as useless, even in connection with quetiapine, is evident from the very fact that in NiK9 the hope was expressed that administration once or twice per day might be sufficient. Additional confirmation of this is provided by the press release reproduced in TM17, according to which the defendant's group of companies had already commissioned another company prior to the priority date to develop a form of administration of Seroquel that would allow an administration frequency of once per day.

37 b) The Patent Court correctly came to the conclusion that the skilled person had to assume on the basis of the data reproduced in NiK9 that the occupancy of the D2 receptors tends towards zero twenty-four hours after the time of the last intake.

38 It is true that NiK9 does not contain any explicit data on receptor occupancy at the time mentioned. However, from the values reproduced there, it appears that the percentage of occupied D2 receptors is 44% two hours after

the last intake and zero twenty-six hours after this time. The conclusion of the Patent Court derived from this that the value was not in a significant range already twenty-four hours after the last intake is not legally objectionable and is not called into question by the objections of the appeal.

39 Admittedly, it cannot be ruled out that the values do not drop linearly, especially since NiK9 shows a drop of fourteen percentage points for the six-hour interval between the first and the second measurement, but only a drop of three percentage points for the subsequent period of four hours. However, even the defendant does not doubt that the further decline is essentially uniform. Its conclusion, drawn on the premise of a linear decline, that twenty-four hours after the time of the last ingestion 4% of the D2 receptors are still occupied, does not contradict the Patent Court's assumption that the occupancy tends towards zero at that time. It is true that NiK9 does not specify the minimum percentage of D2 receptors that must be occupied for quetiapine to have the intended effect. However, in view of the fact that the percentage of occupied receptors is still 30% eight hours after the time of the last intake - i.e., within a period in which a new intake can be expected if the drug is administered three times per day - there is no evidence that a value of 4% also still appeared to be sufficient from a professional point of view, especially since NiK9 shows a clearly different course for the percentage of occupied 5HT2 receptors, which only shows the measured maximum level of 85% eight hours after the time of the last intake and a residual level of 50% twenty-six hours after the time mentioned.

40 c) The Patent Court rightly concluded from this that there were no promising indications from NiK9 that the active ingredient quantity of 450 mg stated there would be suitable for only one administration per day with immediate release.

41 aa) The circumstance pointed out by the defendant and its private expert Prof. Dr. M. that the relatively weak binding to the D2 receptor and the relatively strong drift away from it after the priority date were regarded as possible causes for the effect of quetiapine (HE12 p. 11) does not lead to a different assessment. In particular, it does not follow from this that the skilled person was already aware of these considerations on the priority date.

42 The publication from 1996 cited by the defendant and its private expert Prof. Dr. K. (Kasper et al., D2-Receptor Imaging (SPEC) as a Tool for Measuring the Efficacy and Side-Effect Profile of Treatment With Neuroleptics, Biol Psychiatry 39 (1996), 564, Annex 3 to HE8) did not provide any information on this. It is reported there that no significant relationship between occupancy of D2 receptors and efficacy was found, and that occupancy of these receptors was associated with side effects in the extrapyramidal motor system (EPMS). For Seroquel, however, it is reported that the available preliminary data suggest a comparable level of occupancy to that seen with the related agent clozapine. It does not follow that even extremely low percentages or only short-term occupancy could be sufficient. Rather, the publication itself suggested that the observed associations might be due to the effect on 5HT2 receptors, because risperidone and olanzapine resulted in relatively high occupancy of D2 receptors but still showed rather low side effects.

43 In the publication by Wetzel et al. (Seroquel (ICI 204 636), a putative "atypical" antipsychotic, in schizophrenia with positive symptomatology: results of an open clinical trial and changes of neuroendocrinological and EEG parameters, Psychopharmacology 119 (1995), 231-238, NiK30) also cite the combined and balanced blockade of D2 and 5HT2 receptors as the likely cause of the observed effects of Seroquel and clozapine, and the antagonism to D2 receptors in Seroquel is thought to be rather weak (NiK30 p. 232 top left). Again, there is no evidence from this that a proportionally low occupancy or only short-term occupancy of these receptors may be sufficient.

44 From the publications of Casey ('Seroquel' (Quetiapine): preclinical and clinical findings of a new atypical antipsychotic, Exp. Opin. Ivest. Drugs 1996, 939-957, NiK31), Hirsch et al. (ICI 204 636: A New Atypical Antipsychotic Drug, British Journal of Psychiatry 168 (1996), 45-56, NiK37), and Fleischhacker et al. (A Multicentre, Double-Blind, Randomised Comparison of Dose and Dose Regimens of 'Seroquel' in the Treatment of Patients with Schizophrenia, American College of Neuropsychopharmacology, 34th Annual Meeting (1995), 275, NiK45) do not yield any further findings in this respect.

45 bb) The hope expressed in NiK9 that Seroquel could nevertheless be suitable for administration once or twice a day also does not lead to a different

assessment.

46 This statement in itself reveals certain doubts as to whether an administration frequency of at least twice per day will not prove necessary in the end. In NiK9, moreover, no indications are given as to the concrete results of the study conducted on which the hope regarding an administration only once per day is based and whether it refers to the dose of 450 mg per day administered in the course of the study or to a higher dose.

47 The concept of "drug holidays" cited by the private expert Prof. Dr. M. in this context (HE12 p. 13) is not mentioned in NiK9 and, moreover, contradicts the assessment reproduced there in the introduction, according to which an administration of three or four times per day was considered necessary at that time.

48 cc) In this context, the Patent Court rightly referred in addition to the results of the SAFARI study mentioned in NiK9, which is reported in NiK45 and in a press release from the defendant's group of companies of October 2, 1995 (World opinion leaders on psychiatric disease are updated on benefits of Zeneca's "Seroquel' in treating schizophrenia, TM16).

49 NiK45, while referring to NiK9, as the appeal correctly points out, reflects the hope expressed there that Seroquel might be active if administered once or twice daily. However, according to both publications, the SAFARI study was concerned solely with the question of whether the administration of 450 mg of Seroquel showed the same effects when divided into two administrations per day as when divided into three administrations per day. The positive answer derived from the study thus only refers to the administration of 225 mg twice a day. From this, the Patent Court correctly deduced that there is no evidence from the study of the possibility of using the said immediate-release dose in a single daily administration, and that the authors of the study did not take the hopes expressed in NiK9 in this regard as an opportunity to extend their investigations to this mode of administration.

50 Whether ethical considerations also played a role in the design of the study, as the appeal claims, is irrelevant for the legal assessment. Even if this

should have been the case, it would also follow from this that an administration frequency of only once per day encountered practical difficulties from the point of view of the skilled person and, as a result, did not offer too great a prospect of success.

51 d) As a result, the Patent Court correctly decided that an increase in the dose was in any case not the only promising means from the point of view of the skilled person to be able to reduce the frequency of administration to once a day.

52 aa) Contrary to the opinion of the Patent Court, however, it was not sufficiently clear to the skilled person from the press release reproduced in TM17 alone that the order given by the defendant to develop a new dosage form referred to a retard formulation. The fact that the company commissioned had particular expertise in the development of such formulations may give some indication in this direction. However, when viewed in isolation, it cannot be inferred with sufficient certainty from the communication that this competence was to be used in the contract awarded or at least was relevant to the selection of the contractor. There was only reason to draw conclusions in this direction if there were also reasons from a technical point of view to consider a retard formulation for quetiapine.

53 bb) Such reasons, however, result from the knowledge available at the priority date about the importance of receptor occupancy and plasma levels.

54 As already stated above, there were indeed indications at the priority date that a relatively low percentage for the occupancy of the D2 receptors is sufficient and even rather beneficial. However, there was insufficient evidence to expect that short-term occupancy of these receptors would be sufficient to achieve the intended effects. Against this background, a promising way to overcome the difficulties apparent from NiK9 may have been to increase the dose administered. The risk mentioned by the Patent Court that this could lead to toxic plasma active substance peaks did not rule this out without further ado, especially since the degree of occupancy of the D2 receptors documented in NiK9 was not too high from the outset and there were indications from Annex 3 to HE8 that a higher degree of occupancy need not necessarily lead to harmful

effects if simultaneous occupancy of the 5HT2 receptors remains guaranteed.

55 Nevertheless, at the priority date, the skilled person had reason not to consider a dose increase as the only alternative, because the single administration of a high dose leads to considerable fluctuations of the plasma level and this was, in any case, not desirable from the point of view at that time.

56 (1) According to the findings of the Patent Court, a plasma level that is as uniform as possible is to be regarded as desirable in principle from the point of view of the skilled person.

57 This is consistent with the statements in the description of the patent in suit (para. 2) and is also not fundamentally doubted by the appeal. Its objection that short half-lives, as documented for quetiapine from NiK9 among others, and the associated rapid decrease in plasma concentration do not necessarily stand in the way of an administration frequency of once per day, rather confirms that strong fluctuations in plasma levels are at least a potential problem.

58 (2) Exemplarily, this assessment for neuroleptics occupying the D2 receptors was also expressed in the publication by Tench et al (Steady-state pharmacokinetics of controlled release and immediate release formulations of remoxipride in patients with chronic schizophrenia, Psychopharmacology 101 (1990), 132-136, TM23).

59 In TM23, trials of a sustained-release formulation of remoxipride are reported. The introduction states extrapyramidal symptoms showed a high degree of correlation with neuroleptic dose and plasma levels. Remoxipride has a half-life of four to seven hours and therefore must be administered two to three times daily. A controlled-release formulation had been developed for once-daily administration to avoid potential side effects that might be associated with high peak plasma concentrations (TM 23 p. 132 rSp).

60 This shows that a sustained-release formulation was already considered if undesirable side effects were not necessarily to be expected with a higher dosage, but at least a certain risk existed.

61 A comparable initial situation also existed on the priority date with regard

to quetiapine. Although the publications already discussed above indicated that the degree of occupancy of the D2 receptors is basically rather low with quetiapine and that the simultaneous occupancy of the 5HT2 receptors ensures additional protection against side effects in the extrapyramidal motor system. However, this did not provide sufficient certainty that such side effects would not occur even if the frequency of administration was reduced to once per day and the daily dose was significantly increased for this purpose.

62 (3) From the fact that the generally existing reservations about strongly fluctuating plasma levels for individual active substances have proven to be unfounded, it could not be deduced at the time of priority that this would also be the case for quetiapine due to the lack of relevant findings. From the passage from the textbook by Remington (The Science and Practice of Pharmacy, 19th edition 1995, p. 893, HE13) referred to by the appeal, according to which omeprazole causes a therapeutic effect lasting seventy-two hours despite a short half-life, there were therefore no firm findings as to whether a similar effect could also occur with quetiapine, especially since the long duration of action of omeprazole in HE13 is described as unexpected for an active substance with a short half-life.

63 cc) In view of all this, there was weighty evidence at the priority date that an increase in the dose would not be sufficient to allow a reduction in the frequency of administration to once per day. This prompted the skilled person to look at common alternatives. These included a sustained-release formulation that results in delayed release and thus less variation in plasma levels.

64 dd) The concerns raised by the appeal that the required dose of quetiapine could be too high to be able to produce such a formulation do not in any case weigh sufficiently heavily in view of the dosage of 450 mg per day described as sufficient in NiK9 and NiK45 to refrain from following the suggested path.

65 The dosage information in the patent application for quetiapine (EP 0 240 228 A1, NiK3, p. 4 lines 42-43) cited by the appeal does not lead to a different assessment. It can be left open whether these indications (1.0 mg to 40 mg per day and kilogram of body weight) contain a typographical error with regard to

the upper limit, because the example values also given for a body weight of 50 kg (50 mg to 200 mg) per day indicate an upper limit of 4.0 mg. In any case, subsequent publications such as NiK9 and NiK45 gave the skilled person the reasonable expectation that such a high dosage was not necessary.

66 e) The appeal does not attack the statements of the Patent Court that the use of a gelling agent as well as the additional measures provided for according to the auxiliary requests were suggested by the state of the art. Legal errors or concrete circumstances which could give rise to doubts as to the correctness and completeness of the findings made by the Patent Court are not apparent in this respect.

67 IV. The decision on costs is based on Sec. 121(2) Patent Act and Sec. 97 Code of Civil Procedure.

Meier-Beck Gröning Bacher

Deichfuß Kober-Dehm

Previous instance:
Federal Patent Court, judgment of 13 November 2012 – 3 Ni 43/10 (EP) connected to 3 Ni 24/11 (EP) –