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Datasheet for the decision of 5 November 2013

Case Number: T 0598/12 - 3.3.02

Application Number: 03017743.0

Publication Number: 1380301

IPC: A61K 31/565, A61K 31/585, A61P 15/00

Language of the proceedings: EN

Title of invention:
Pharmaceutical combination of ethinylestradiol and drospirenone for use as a contraceptive

Patent Proprietor:
Bayer Pharma Aktiengesellschaft

Opponents:
Teva Pharmaceutical Industries LTD.
Sandoz International GmbH
Helm AG
Gedeon Richter Plc.
Laboratories Léon Farma, S.A.

Headword:
Tablets comprising ethinylestradiol and drospirenone

Relevant legal provisions:
EPC Art. 100(c), 123(2), 76(1), 84

Keyword:
"Main request and auxiliary request 1: added matter (Yes)"

Decisions cited:
G 0002/10, T 0007/07

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0598/12 **-** 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 5 November 2013

Appellant: (Patent Proprietor)	Bayer Pharma Aktiengesellschaft Müllerstrasse 178 D-13353 Berlin (DE)
Representative:	Plougmann & Vingtoft A/S Rued Langgaards Vej 8 DK-2300 Copenhagen S (DK)
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Respondent 3: (Opponent 3)	Helm AG Nordkanalstrasse 28 D-20097 Hamburg (DE)
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Representative:	Schön, Christoph Dr. Schön & Partner Bavariaring 26 D-80336 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 30 January 2012 revoking European patent No. 1380301 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman: U. Oswald
Members: M. C. Ortega Plaza
L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 380 301, based on European patent application No. 03017743.0 which was filed as a divisional application of application No. 00953387.8, which was filed as international patent application published as WO 01/15701 (parent application as filed), was granted with twenty-three claims.

Claim 1 as granted read as follows:

"1. A pharmaceutical composition comprising, as a first active agent drospirenone in an amount corresponding to a daily dosage, on administration of the composition, of from about 2 mg to 4 mg, and as a second active agent, ethinylestradiol in an amount corresponding to a daily dosage of from about 0.01 mg to 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients, wherein at least 70% of said drospirenone is dissolved from said composition within 30 minutes, as determined by USP XXIII Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate."

Dependent claims 10 and 11 as granted read as follows:

"10. The composition according to any of claims 1 to 9, wherein said composition is in the form of an oral dosage form."

"11. The composition according to claim 10, wherein said oral dosage form is a tablet, pill or capsule."

II. Oppositions were filed and revocation of the patent in its entirety was requested, in particular pursuant to Article 100(c) (the subject-matter of the patent extends beyond the content of the application, or earlier application, as filed), 100(a) (lack of novelty and lack of inventive step) and 100(b) EPC (lack of sufficiency of disclosure).

III. The following documents were cited *inter alia* in the opposition and appeal proceedings:

D3 Cohen et al., Pharmaceutical Research, vol. 7, No 10, 983-987, 1990
D12 Guidance for Industry. Dissolution Testing of Immediate Release Solid Oral Dosage Forms, US Department of Health and Human Services, Food and Drug Administration, 1997
D15 Melia and Davis, Aliment. Pharmacol. Therap., 3, 513-525, 1989
D26a experimental data (reworked example 2 of DE 19652196)
D26b experimental data (obtained from reworked example 2 of DE 19652196)
D43 Remington's Pharmaceutical Sciences, 18th edition, 1990, Chapter 31, Dissolution, pages 589-602
D45 Supplementary data
D46 Supplementary in vitro dissolution data for DRSP
D46a Working report
D54 WO 98/06738
D69 FIP Guidelines for Dissolution Testing of Solid Oral Products, Pharm. Ind., 57(5), 362-369, 1995
D74 Thibert and Tawashi, Microspheres, Microcapsules and Liposomes, MML Series, vol. 1, 327-328, 1999

D90 Copy of SGS Certificate of analysis, Institut Fresenius, comparative dissolution profiles for Yasmin^{R} tablets.

IV. The following UK national decision was also cited:

D75 "Gedeon Richter PLC v. Bayer Schering AG", High Court of Justice, Chancery Division, Patent Court, [2011] EWHC 583 (Pat), dated 17 March 2011.

V. The present appeal lies from a decision of the opposition division revoking the patent (Article 101(3)(b) EPC).

VI. The opposition division considered that the claims of the main request and auxiliary requests 1 to 3 filed with the letter of 30 September 2011 contained added matter within the meaning of Articles 100(c), 76(1) and 123(2) EPC. However, in the opposition division's opinion the requirements of Article 123(3) EPC were met.

VII. The patent proprietor (appellant) lodged an appeal against said decision. With its grounds of appeal it filed a new main request and auxiliary request 1, as well as documents D111 and D112. It requested that the decision under appeal be set aside and the case be remitted to the department of first instance for further prosecution on the basis of that the main request or, alternatively, auxiliary request 1.

Claim 1 of the main request reads as follows:

"1. A tablet comprising, as a first active agent drospirenone in an amount corresponding to a daily

dosage, on administration of the tablet, of 3 mg, and as a second active agent, ethinylestradiol in an amount corresponding to a daily dosage of from about 0.01 mg to 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients, wherein at least 70% of said drospirenone is dissolved from said tablet preparation containing 3 mg drospirenone within 30 minutes, as determined by USP XXIII Paddle Method II using 900 ml water at 37°C as the dissolution media and 50 rpm as the stirring rate".

Claim 1 of auxiliary request 1 reads as follows:

"1. A tablet comprising, as a first active agent drospirenone in an amount corresponding to a daily dosage, on administration of the tablet, of 3 mg, and as a second active agent, ethinylestradiol in an amount corresponding to a daily dosage of from about 0.01 mg to 0.05 mg, together with one or more pharmaceutically acceptable carriers or excipients, wherein drospirenone is provided in a form that promotes rapid dissolution so that at least 70% of said drospirenone is dissolved from said tablet preparation containing 3 mg drospirenone within 30 minutes, as determined by USP XXIII Paddle Method II using 900 ml water at 37°C as the dissolution media and 50 rpm as the stirring rate".

VIII. Opponents O1 (respondent 1), O2 (respondent 2), O3 (respondent 3), O4 (respondent 4) and O5 (respondent 5) filed counter-arguments to the patentee's appeal. They requested that the appeal be dismissed. Respondent 4 filed with its reply of 24 October 2012 documents D113 to D119. In addition to the objections of unallowable added-matter within the meaning of Articles 100(c),

123(2) and 76(1) EPC raised by all respondents, respondents 2 and 5 also raised objections under Article 84 EPC against claim 1 of auxiliary request 1 with their responses to the grounds of appeal dated 23 and 24 October 2012, respectively.

IX. The board sent on 4 June 2013 a communication pursuant to Article 15(1) RPBA as an annex to the summons to oral proceedings.

In said communication the board informed the parties that in the oral proceedings it would assess whether or not the claims of the main request and auxiliary request 1 filed with the grounds of appeal included added matter, i.e. matter not directly and unambiguously disclosed in the application and the earlier application as filed, and that the assessment of compliance with the requirements of Articles 123(3) and 84 EPC was also within the framework of the discussion at the oral proceedings.

X. With a letter dated 17 June 2013 the appellant filed a further document, D120 (declaration of Mr Heller dated 12 April 2013).

XI. With a letter dated 30 July 2013 the appellant filed a "response to the respondents' comments" to the grounds of appeal as well as observations regarding the board's communication. It also filed documents D58a, D121 and D122.

XII. With a letter dated 25 September 2013 respondent 2 filed further observations in relation to Article 123(3) and Article 76(1) EPC.

XIII. With a letter dated 7 October 2013 respondent O5 filed further observations *inter alia* in relation to Articles 100(c), 123(3) and 84 EPC.

XIV. With a letter dated 7 October 2013 respondent 3 announced that it would not be attending oral proceedings but maintained its written submissions and requests.

XV. Third-party observations in relation to novelty were filed on 29 October 2013.

XVI. Oral proceedings took place on 5 November 2013.

XVII. The appellant's arguments, as far as relevant for the present decision, may be summarised as follows.

(a) *Main request, Articles 100(c), 123(2), 76(1) EPC*

The opposition division had found that the specific dissolution profile defined in the second paragraph on page 4 of the application as filed was linked to a certain micronized form of DRSP. However, this was a formalistic approach which did not make use of the sound principle that the specification be read by the skilled person in the field. The gold standard to be applied could be found in the Enlarged Board of Appeal decision G 2/10, OJ EPO 2012, 376, under the heading "The basic principle underlying Article 123(2) EPC, in the jurisprudence of the Enlarged Board of Appeal" (point 4.3 of the reasons). Amendments could only be made within the limits of what a skilled person would derive directly and unambiguously from the whole of the

application as filed, using his common general knowledge. In this context, the appellant also quoted technical board of appeal decision T 0667/08 of 20 April 2012, in particular the catchword and point 4.4.4 of the reasons: "*It is therefore essential, when deciding on issues of added subject-matter, to identify the actual teaching conveyed by the original disclosure, i.e. the technical information that the skilled person reading the original disclosure would have derived from its content (description, claims, drawings) considered in its entirety. This approach might lead to the identification of subject-matter which has not been explicitly revealed as such in the application as filed, but nevertheless derives directly and unambiguously from its content. Literal support is not required by the wording of Article 123(2) EPC.*"

Therefore, one should not use a semantic approach and the text in the application as filed should not be interpreted literally. What counted was whether or not the skilled person was presented with different technical information from that in the application as filed. Therefore, it had to be investigated whether the skilled person would consider the feature concerning the *in vitro* dissolution profile as an independent feature or only in combination with other features. The skilled person, i.e. the pharmaceutical technologist, knew that several formulations could achieve the same profile.

In this context the appellant cited document D15, a review article relating to "mechanisms of drug release from tablets and capsules and dissolution", and in particular the section on pages 518 and 519 entitled

"Strategies for enhancing drug dissolution rates from tablets and capsules". The appellant submitted that in table 1, page 519 several forms for promoting rapid dissolution were mentioned, in addition to micronization of the drug substance. Moreover, document D43, a Handbook about Pharmaceutical Sciences, outlined in its chapter entitled "Dissolution", the factors affecting the rate of dissolution (page 591). Among those factors relating to the physiochemical properties of the drug, micronization and crystalline state of the drug were mentioned. Additionally, page 601 of document D43 mentioned that "Depending on how slow the intrinsic dissolution rate is, the formulator may choose to improve it by micronization, complex formation, derivatization or any other techniques generally utilised for enhancing the dissolution rate of insoluble drugs."

In relation to the respondents' arguments about *in vivo*/*in vitro* dissolution the appellant cited three documents: D3, D12 and D69. The term "dissolution" was used in documents D12 and D69, although dissolution *in vitro* was meant. Document D12 concerned a guidance for dissolution testing for immediate release dosage forms and provided general recommendations for dissolution testing, as well as approaches for dissolution specifications (paragraph under the heading "Introduction"). Document D12 showed that new drug applications contained bioavailability data and *in vitro* dissolution data for characterising the drug product. Thus, the skilled person knew that, in practice, the data of importance were *in vivo* bioavailability data and *in vitro* dissolution data. The definitions for slowly dissolving or poorly water

soluble drugs (BCS class 2) on page 5 of document D12 were completely in line with the dissolution profile on page 4 of the parent application as filed. The appellant also cited page 5, lines 7 to 10 of the parent application as filed, which were dedicated to the second active compound (ethinylestradiol), in order to support the argument that the dissolution profile of DRSP on page 4 was not restricted to a particular micronized form characterised by a certain surface area and particle size distribution. Furthermore, it pointed to the profile for the first and second case in document D3, page 984, right-hand column, lines 22 ff. It also drew attention to Table 1 for the test conditions: water, apparatus 2, 50 rpm, and first case dissolution profile (in no less than 76 monographs) and to document D12, Appendix A: "the volume of the dissolution medium is generally 500, 900, or 1000 mL".

Therefore, the skilled person was aware from his common general knowledge of numerous methods for providing a rapid dissolution profile, *inter alia* by means of micronization, crystal forms, complexation and use of surfactants, and he knew which criteria were recommended for application to rapid dissolution in immediate release forms. The skilled person also knew that for each particular drug substance a more precise definition of the dissolution profile was needed. It was in the light of this general knowledge of the skilled person that the specification of the parent application as filed had to be read. Thus, the first paragraph on page 4 of the parent application as filed defined the gist of the invention, and the profile in the second paragraph on page 4, lines 16 to 20 applied directly to that general teaching. The passage on

page 4, lines 26 to 31 explained that a correlation between the *in vitro* dissolution rate and the *in vivo* behaviour lead to the outcome of good bioavailability for DRSP. There was no mention in that particular passage of a particular micronized form or of DRSP sprayed on the surface of particles of an inert carrier. The rapid dissolution in paragraph 1 on page 4 was to be defined by the dissolution profile in paragraph 2 on page 4. The third paragraph concerned the theory why there was an *in vivo*/*in vitro* correlation.

The appellant further referred to page 9, line 10 of the parent application as filed, where it was stated that "the composition of the invention may be formulated in any manner known in the pharmaceutical art", and to the examples. In particular, example 2 mentioned the USP XXIII Paddle Method using an ESP Dissolution Test Apparatus 2 as the test for determining the dissolution of DRSP from the tablets. This test was also used in example 3 for determining the rate of dissolution of ethinylestradiol and the active agent was dissolved within 30 minutes.

In the decision underlying the present appeal the opposition division had made an attempt to define the common general knowledge of the skilled person (pages 12 and 13) but its decision was contradictory in relation to the division's reading of the expression "rapid dissolution" and the conclusions reached (generic *versus* specific) by the skilled person.

As shown by the cited general prior-art documents, the definitions given in the parent application as filed for *in vitro* dissolution rate were not alien to the

skilled person who knew that a particular dissolution profile for an active substance was not restricted to a specific form, and thus would never have read the dissolution profile appearing on page 4 in a restrictive way. In this context the appellant cited document D74, and the chapter entitled "Micronization of Pharmaceutical Solids", page 328, for the definition of the term "micronization": "To the pharmaceutical formulator, it means obtaining fine particles smaller than 20 µm, and preferably smaller than 5 µm". This definition was in line with the definition of the particle size on page 4 of the parent application as filed.

Asked by the board in how far its arguments applied to the features defined in claim 1 of the main request, the appellant replied that the skilled person would read claim 1 in the light of what was said on page 4 of the parent application as filed.

Furthermore, the appellant also submitted that claim 1 derived from claim 1 as originally filed, in which the definition of rapid dissolution was introduced. If the definition in claim 1 was not identical to that given in documents D3 and D12, this was due to the fact that these documents concerned recommendations and, as explained in document D12, the dissolution profile had to be more specific in relation to a particular active drug.

Asked by the board whether it confirmed that claim 1 of the main request also encompassed tablets for which the dissolution profile of DRSP was attained by means of particular excipients or additives and not necessarily

by means of a particular rapid dissolution form of DRSP, the appellant answered in the affirmative. Furthermore, it drew attention to the use of a surfactant, as a possible option mentioned in document D15. The general teaching in the parent application as filed was that rapid dissolution of DRSP gave rise to good bioavailability. Although the use of brackets in the sentence on page 4, lines 11 to 15 of the parent application as filed could be regarded as being inept from a linguistic point of view, the essential point was how the skilled person would have read the specification. It also cited claim 7 of the parent application as filed.

The appellant contended that the skilled person reading the parent application as filed found a basis for the general teaching claimed in claim 1, making use of his common general knowledge. In this context, it referred to the favourable conclusions in relation to added matter in UK national decision D75 (in particular, it cited paragraph 75), which dealt with the British part of EP 1 380 301 (i.e. it was the same case). Although the appellant acknowledged that this decision was not binding on the board, the fact that UK decision D75 was not merely a linguistic analysis of the parent application as filed was highlighted by Lord Justice Kitchin, who presided over the appeal from the decision in D75. Moreover, in Special Edition 1, 2013, of the Official Journal of the EPO (16th Symposium of European Patent Judges), Lord Kitchin stressed that the UK approach concerned the strict test that "matter will be added unless it is clearly and unambiguously disclosed in the application either expressly or implicitly" and "the UK approach was therefore, in essence, the same as

that explained by the Enlarged Board in G 2/10 of 30 August 2011". Board of appeal decision T 0007/07 did not represent *res judicata* for the present appeal case since the facts were not the same and the claims were different. Decision T 0007/07 did not have a higher ranking than other board of appeal decisions for the present case. Decision T 0007/07 could never replace the analysis of the disclosure in the light of the principles constituting the gold standard mentioned in G 2/10. Additionally, decision T 0007/07 decided on the disclosure of a particular embodiment, but not on that of the general teaching.

The appellant also stressed that the passage in the third paragraph on page 4 concerned an explanation why there would be a correlation between *in vitro* dissolution and bioavailability. Naturally, it was not denied that actual studies on bioavailability had to be performed. However, no single document had been cited in which the dissolution rate was measured *in vivo*. Example 4 of the specification concerned the tablets disclosed in the previous examples.

The appellant submitted that respondent 1's submission that the dissolution profile obtained in the *in vitro* test in water was not representative for the dissolution under the acidic conditions of the stomach was not correct, as shown by the comparative studies in document D90. It further mentioned the supplementary dissolution data in documents D45, D46, D46a.

As regards respondent 5's reference to claims 8 and 9 as originally filed, the appellant stated that it was the description which should be used to interpret the

claims and not the other way round. Additionally, the appellant cited board of appeal decision T 637/09 of 20 March 2013, taken by the same board as in the present case, which made a clear distinction as to whether something was released from a tablet or actually dissolved in a *medium* (page 65). The experimental results submitted with documents D26a and D26b reproducing examples with DRSP sprayed on inert carrier particles had shown such release profiles of >70% within 30 minutes.

(b) *Auxiliary request 1, Articles 100(c), 123(2), 76(1) and 84 EPC*

The arguments submitted in relation to the main request applied *mutatis mutandis* to claim 1 of auxiliary request 1.

Moreover, if claim 1 of the main request were considered to contain added matter because only certain forms of DRSP led to rapid dissolution, then the amendment in claim 1 of auxiliary request 1 was a remedy for that situation: in claim 1 of auxiliary request 1 only those forms of DRSP which had an impact on the dissolution profile were claimed. In this context it again cited document D15, page 519, Table 1, particle size and crystal form modifications. It explicitly mentioned micronization, polymorphic forms, molecular disperse forms, and complexation with cyclodextrines. It also cited document D43 and the first category mentioned which concerned the physiochemical properties of the drug, which discussed micronization (page 591, right-hand column) and molecular dispersion into a soluble carrier such as a

PVP solution (page 592, right-hand column) as methods usually employed for the enhancement of the dissolution rate of insoluble drugs.

The expression used in claim 1 of auxiliary request 1 was understood by the skilled person as relating to the options generally known in the art. The skilled person knew in the light of the description how to provide DRSP that promoted such a dissolution profile. The definition profile for DRSP was clear and it was also clear how to determine it.

XVIII. The respondent's arguments, as far as relevant for the present decision, may be summarised as follows.

(a) *Main request, Articles 100(c), 123(2), 76(1) EPC*

Respondent 1 referred to the case law of the boards of appeal of the EPO in relation to the standard of proof for the allowability of amendments under Articles 123(2) and 76(1) EPC. It submitted that the EPO applied strict standards and argued that if there were doubts whether or not a particular amendment was derivable from an application as filed, the amendment was not allowable since it must be "unambiguously" derived. The amendments in the present case were not directly and unambiguously derivable from the parent application as filed. The skilled person would understand that other methods were known, but the specification only disclosed a particular micronization form for achieving the dissolution profile defined in the second paragraph on page 4. In fact, page 4 of the parent application as filed disclosed in the second paragraph that drospirenone (DRSP) was provided in micronized form and

that with a particular micronized DRSP (defined by means of surface area and particle size distribution) a rapid dissolution of the active compound occurred *in vitro*. The profile for this particular "rapid dissolution" attained *in vitro* was defined. Therefore, the parent application as filed disclosed that the rapid dissolution profile determined by the USP XXIII Paddle Method in the second paragraph on page 4 was intimately and intrinsically linked to a particular micronized form of DRSP.

Respondent 1 submitted that the appellant had maintained that the particular definition on page 4, second paragraph, concerning a rapid dissolution applied to every mention of "rapid dissolution", in particular to that at the end of the first paragraph on page 4. However, there were at least two possible dissolution rates: one *in vitro* and one *in vivo*. The first paragraph on page 4 related to dissolution *in vivo* since it referred to bioavailability, which was something which only occurred *in vivo* in the body and which was to be determined by using test methods completely different from the *in vitro* test defined in the second paragraph on page 4. Therefore, the definition in the second paragraph on page 4 did not apply to each and every mention of "rapid dissolution". This was made clear in the third paragraph on page 4, which explicitly mentioned a dissolution rate *in vitro* and a dissolution rate *in vivo* on oral administration of the compound. The opposition division's findings were correct. Moreover, the specific paddle method test defined in the second paragraph on page 4 did not represent the conditions *in vivo*, in the stomach, and thus there was not necessarily a correlation between

the *in vivo* dissolution rate and the dissolution rate so obtained. Document D69, table 3, made it clear which were the possible reasons for poor *in vivo/in vitro* correlation and mentioned as a fundamental reason that "No *in vitro* test is able to model *in vivo* dissolution". In fact, the parent application as filed did not show whether an *in vivo/in vitro* correlation actually existed. Example 4 referred to bioavailability of DRSP and ethinylestradiol from certain tablets but it was not specified whether these were the tablets prepared and tested in the previous examples.

Moreover, decision T 0007/07 of 7 July 2011 (board 3302 in another composition), which concerned the patent deriving from the parent application, had decided that the feature (d), i.e. the dissolution profile *in vitro*, was disclosed "*only in combination with a specific form of micronisation for drospirenone*" and thus, its introduction into the claim amounted to "an unallowable generalisation" (page 25).

Therefore, the introduction of said feature into claim 1 of the main request, which was not restricted to a particular micronized form of DRSP, was not allowable under Article 100(c) EPC, in conjunction with Article 76(1) EPC, for analogous reasons to those given in decision T 0007/07. Respondent 1 clarified that it was not arguing that it was a case of *res judicata* because, *inter alia*, the parties were different, but that was no reason for the patentee to get a better result when the facts remained the same. Respondent 1 submitted that High Court decision D75 predated decision T 0007/07, and thus had little relevance. Moreover, respondent 1 submitted that the national

judges in D75 did not necessarily use the same standard as the EPO for assessing added matter, as alleged by the appellant in its letter dated 30 July 2013. Proof was that in decision D75, under the headings "Added Matter", "Law", not a single decision of the Enlarged Board of Appeal or of the technical boards of appeal of the EPO had been cited. The British courts had developed different standards and different "tests" from those of the EPO.

Moreover, decision G 2/10, which related to claims containing a disclaimer, other Enlarged Board of Appeal decisions and opinions were also cited in point 4.3 (*inter alia* opinion G 3/89 and decision G 11/91, OJ EPO 1993, 117 and 125, respectively, and decision G 1/93, OJ EPO 1994, 541) in relation to the standard for amendments.

Respondent 2 endorsed respondent's 1 arguments. Additionally, it stated that the aim of the patent was to increase the bioavailability of the active compounds and this aim was attained either by micronization or by spraying onto the surface of inert carrier particles. However, when the active compound was DRSP then it had to be provided in a particular micronized form, as defined in the second paragraph on page 4. This passage could never serve as an allowable basis for a generic composition, which was defined independently from any method of providing a particular micronized form of one of the active compounds.

Additionally, the dissolution profile defined in claim 1 of the main request was not the same as the profile in document D3 (75% had to be dissolved and not

70%) and both were also different from the profile for poorly soluble drugs defined in document D12. Therefore, there was no such thing as a homogeneous definition for rapid dissolution. The parent application as filed did not disclose as general teaching that the particular *in vitro* profile in the second paragraph was attainable by any possible means; what it disclosed was that the particular *in vitro* dissolution profile was attained with a particular micronized form of DRSP. Document D15 disclosed that improvement of the dissolution properties of poorly soluble drugs given orally could be achieved by means of suitable additives. However, the teaching in the parent application as filed did not go in this direction.

Respondent 4 shared the arguments submitted by respondents 1 and 2 and further submitted that the specific dissolution profile *in vitro* was disclosed for DRSP only in connection with a particular micronized form and not with the sprayed option.

Respondent 5 further stressed that the disclosure in the first paragraph on page 4 concerned bioavailability and thus, the dissolution was *in vivo*, whereas in the second paragraph the dissolution was *in vitro*. Document D3, which had been cited in the appellant's last submissions (letter dated 30 July 2013) as reflecting the common general knowledge of the skilled person at the time of the patent in suit, showed that the skilled person was aware that *in vitro*/*in vivo* correlations were in principle possible, but then several correlation methods were possible and certain parameters had to be considered for the comparison. Taking the disclosure in the application as filed in

the light of his common general knowledge, the skilled person would not have concluded that there was a correlation in vitro/in vivo so that the *in vitro* dissolution profile and the *in vivo* dissolution profile were the same.

Respondent 5 also pointed to claims 8 and 9 of the parent application as filed, which related to the dissolution *in vivo* since the dissolution rate was "after administration". Therefore, there were two different dissolution profiles disclosed in the parent application as filed: one *in vitro* and one *in vivo*. Moreover, even if it were considered that example 4 referred to the tablets prepared in example 1 and tested *in vitro* in example 2, those tablets contained micronized DRSP.

According to its written submissions, respondent 3 shared the views of the opposition division. Additionally, respondent 3 submitted that the appellant's arguments did not disprove the opposition division's findings that the amendments were not unambiguously and directly derivable from the application as filed. Respondent 3's arguments submitted in writing are analogous to those submitted by respondents 1, 2, 4 and 5.

(b) *Auxiliary request 1, Articles 100(c), 123(2), 76(1) and 84 EPC*

Respondents 1, 2, 4 and 5 stated that the reasons they had submitted in relation to the main request applied *mutatis mutandis* to claim 1 of auxiliary request 1.

Respondent 1 stressed that the dissolution profile was intimately linked to a specific micronized form of DRSP. There might be some *in vivo/in vitro* correlation, but this was not shown in the application as filed.

Respondents 2 and 4 objected to the clarity of the amendment "*wherein drospirenone is provided in a form that promotes rapid dissolution so that...*" introduced in claim 1 of auxiliary request 1 (Respondent 2 also referred to its written submissions filed with the letter dated 23 October 2013). They submitted that this was an attempt to define the invention by the result-to-be-achieved. The application as filed disclosed two alternative embodiments for providing DRSP in order to promote rapid dissolution: micronization and spraying on the surface of inert carrier particles. There was no justification for defining the invention by means of the result-to-be-achieved. Additionally, respondent 2 stated that there was a lack of clarity since the application did not contain a clear and complete definition of how to determine and achieve that aim functionally defined in the claim.

Respondent 5 further submitted that the parent application as filed did not provide a clear basis for the combination of *in vivo* and *in vitro* dissolution profiles and that the amended claim concerned requirements and a finalised conclusion which were not directly and unambiguously disclosed in the parent application as filed.

XIX. The appellant requested that the decision under appeal be set aside and the case remitted to the department of first instance for further prosecution on the basis of

the main request or, alternatively, of auxiliary request 1 filed with the grounds of appeal.

The respondents requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *General remarks*

2.1 The patent in suit derives from European patent application 00953387.8 filed as an international application which was published as WO 01/15701 (parent application as filed).

The parent application, which was granted as EP-B1-1214076, underwent opposition proceedings and was revoked by decision T 0007/07 of 7 July 2011 (taken by this board in another composition).

2.2 The documents concerning the description and examples as originally filed are identical for the parent application and its divisional (i.e. the application from which the patent in suit derives). However, the sets of claims of the two applications as filed differ from each other.

3. National decision D75 has no binding effect on the board in the present appeal case. The parties are not the same and the facts and evidence before the national court are not necessarily the same as those in the

present case for which the present parties have had an opportunity to comment.

4. *Main request (Articles 100(c), 123(2) and 76(1) EPC)*

4.1 According to the principles set out in the jurisprudence of the Enlarged Board of Appeal, an amendment can only be found allowable under Articles 123(2), 76(1) EPC if it is made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge and seen relatively and objectively to the date of filing, from the whole of the application as filed (G 2/10 point 4.3 of the reasons, under the heading "The basic principles underlying Article 123(2) EPC in the jurisprudence of the Enlarged Board").

One essential aspect is to investigate whether the amendments present the skilled person with technical information which is not directly and unambiguously disclosed in the application as filed.

Whether the skilled person is presented with new information not directly and unambiguously disclosed in the application as filed depends on how he or she would understand the amended claim and on whether, using common general knowledge, he or she would regard that subject-matter as at least implicitly disclosed in the application as filed (G 2/10, point 4.5.2 of the reasons).

4.2 Claim 1 of the main request relates to a tablet comprising two active ingredients: drospirenone, DRSP, (3 mg) and ethinylestradiol (0.01 mg to 0.05 mg)

together with one or more pharmaceutically active carriers and excipients. The tablet claimed in claim 1 is further characterised in that "at least 70% of said drospirenone is dissolved from said tablet preparation containing 3 mg drospirenone within 30 minutes, as determined by USP XXIII Paddle Method II using 900 ml water at 37°C as the dissolution media and 50 rpm as the stirring rate."

Claim 1 of the main request does not have a *verbatim* basis in the parent application as filed. Furthermore, claim 1 encompasses in its broadest technically meaningful sense tablets in which the particular dissolution profile is attained by means of the other constituents of the tablet, i.e. carriers and/or excipients, and in which the active ingredient DRSP does not necessarily need to be itself in a form which promotes rapid dissolution.

Therefore, in order to assess added matter in claim 1 of the main request, it has to be investigated whether or not this technical information encompassed by the claim (namely that the specific dissolution profile defined in the claim may be attained by means of carriers and excipients and not necessarily by means of the physical form of the active ingredient DRSP) is directly and unambiguously disclosed in the parent application as filed.

4.3 The parent application as filed does not explicitly disclose tablets in which the particular dissolution profile defined in the claim is attained by means of the choice of carriers and excipients, without

providing first the active ingredient DRSP in a physical form capable of promoting rapid dissolution.

4.3.1 The first paragraph on page 4, under the heading "Detailed disclosure of the invention", has been repeatedly referred to by the appellant as essential for the basis of the amendments. The full paragraph reads as follows: "Drospirenone, which may be prepared substantially as described in e.g. US 4 129 564 or WO 98/06738, is a sparingly soluble substance in water and aqueous buffers at various pH values. Furthermore, drospirenone is rearranged to an inactive isomer under acid conditions and hydrolysed under alkaline conditions. To ensure good bioavailability of the compound, it is therefore advantageously provided in a form that promotes rapid dissolution thereof."

4.3.2 This first paragraph on page 4 is immediately followed by the text in the second paragraph: "It has surprisingly been found that when drospirenone is provided in micronized form (so that particles of the active substance have a surface area of more than 10,000 cm^2/g, and the following particle size distribution as determined under the microscope: not more than 2 particles in a given batch with a diameter of more than 30 µm, and preferably ≤ 20 particles with a diameter of ≥ 10 µm and ≤ 30 µm) in a pharmaceutical composition, rapid dissolution of the active compound from the composition occurs in vitro" (page 4, lines 11 to 16).

Further on in the second paragraph on page 4, it is stated that: "Instead of providing the drospirenone in micronized form, it is possible to dissolve it in a

suitable solvent, e.g. methanol or ethyl acetate, and spray it onto the surface of inert carrier particles followed by incorporation of the particles containing drospirenone on their surface in the composition" (page 4, lines 20 to 24).

4.3.3 Therefore, the specification on page 4 explicitly discloses, as the generic embodiments of the intended invention, micronization of the active ingredient DRSP and particles in which the active ingredient DRSP is sprayed onto the surface of an inert carrier.

4.3.4 Moreover, the addition of other carriers or excipients is disclosed in the parent application as filed only in so far as they are added to the formulation in order to constitute the final composition or dosage form (tablets, pills or capsules) (see page 9, second paragraph), in which the active ingredients are provided according to the alternatives disclosed in the application (paragraph 2 of page 4 for DRSP and the paragraph bridging pages 4 and 5 for ethinylestradiol). These alternatives always imply the presence of the active ingredients in a certain physical form: micronized or sprayed onto the surface of inert carrier particles; and this only in so far as these forms are capable of promoting rapid dissolution of the compounds. After the active ingredients are provided in such forms, carriers or excipients may then be chosen to "obtain a **more** rapid rate of dissolution" (page 5, lines 11 and 12, page 9, second paragraph).

The examples do not give more information to the skilled person, since they relate to the preparation of tablets containing DRSP and ethinylestradiol, both in

micronized form (example 1), to dissolution tests from those tablets (examples 2 and 3) and to bioavailability studies from tablets which are not explicitly characterised (example 4), and, finally, to contraceptive efficacy studies (example 5).

4.3.5 Therefore, there is no disclosure in the parent application as filed for formulations, compositions or dosage forms, in particular tablets, from which a rapid dissolution profile of the active ingredient DRSP is obtained owing to the merit of choosing the appropriate excipients only, and without providing first the active ingredient DRSP in a specific physical form capable of promoting rapid dissolution.

This finding is not modified by the content of the third paragraph on page 4, which merely concerns the information that *in vitro/in vivo* correlation is in principle possible for DRSP administered orally.

4.3.6 The remaining question now is whether or not the skilled person using his common general knowledge would regard that subject-matter (i.e. tablets of DRSP and ethinylestradiol from which the particular dissolution profile of DRSP defined in claim 1 is attained by means of the choice of carriers, excipients and/or other additives, without the help of particular physical forms for DRSP capable themselves of promoting rapid dissolution) as directly and unambiguously implicitly disclosed in the parent application as filed.

It has to be stressed that it is not to be investigated whether a certain technical information derives from the prior-art knowledge in the field. What has to be

judged is whether the notional skilled person working in the field would consider something as **directly and unambiguously** implicitly disclosed in the light of his common general knowledge. The assessment of what information is implicitly disclosed in an application cannot go beyond the limits of what the skilled person would objectively understand to be a direct and unambiguous consequence of the explicit disclosure in the particular case. Going beyond that would allow the introduction of added matter, after the date of filing of the (parent) application, for which there is no unambiguous disclosure in the (parent) application as filed, contrary to the provisions of Articles 123(2) and 76(1) EPC. Moreover, when performing this assessment, the common general knowledge cannot serve to enlarge or replace in a subjective or artificial manner, the actual content of the specification.

4.3.7 In the present case, the parent application as filed leaves no space for interpretation of the clear disclosure concerning the way carriers and excipients are to be employed according to the disclosed invention, namely either as inert carrier particles to support on their surface sprayed DRSP or ethinylestradiol, or as commonly known carriers and excipients expected to facilitate (and not interfere negatively with) the dissolution rate obtainable from the physical forms of the active ingredients provided according to the parent application as filed.

It is generally known that when determining the dissolution rate of drugs from solid dosage forms under standardised conditions, one has to consider several physicochemical processes in addition to those

concerning the dissolution of pure chemical substances. "These include the wetting characteristics of the solid dosage forms, the penetration ability of the dissolution medium into the dosage forms, the swelling process, disintegration and deaggregation" (document D43, passage bridging pages 590-591).

4.3.8 However, the fact that the skilled person in the field of pharmaceutical formulations and dosage forms is aware that immediate release dosage forms (i.e. dosage forms capable of obtaining dissolution profiles at least comparable to those defined in document D3, pages 983 to 985 and table I) may be generically prepared using particular excipients, carriers or additives, without necessarily having to provide first the active ingredient(s) in a distinct physical form, does not form part of the disclosure of tablets containing DRSP and ethinylestradiol which is directly and unambiguously derived, either explicitly or implicitly, from the parent application as filed.

The reasons are that the skilled person understands that the teaching disclosed in the parent application concerning the actual dosage form disclosed, i.e. the tablets containing the specific active ingredients (DRSP and ethinylestradiol), relates only to the approach in which distinct physical forms for the sparingly soluble substance DRSP are provided before constituting the actual dosage form by choosing suitable excipients commonly known in the art.

4.3.9 Document D15 reflects common general knowledge of the skilled person about the importance of drug dissolution to oral therapy and the physical process of dissolution.

It also reflects the general existence of several approaches to improving the dissolution properties of poorly soluble drugs to be given orally. However, this does not mean that the parent application as filed discloses directly and unambiguously, either explicitly or implicitly, each and every one of the approaches, mentioned in document D15 only in general terms, for the specific active ingredient DRSP.

The investigation of the actual disclosure in a patent application as filed pursuant to Article 100(c) EPC cannot turn into an investigation of obviousness or a search for obvious alternatives of the actual disclosure in the light of general prior-art documents. Such an investigation would be part of the assessment of inventive step under Article 56 EPC, if the skilled person is looking to solve a certain technical problem (e.g. to ensure good bioavailability) without making use of his inventive skills, but it cannot be taken as a valid approach for the investigation of implicit disclosure directly and unambiguously derivable from an application as filed within the meaning of Articles 123(2) and 76(1) EPC.

Apart from that, the different (and separately mentioned) general approaches listed in document D15 for improving the solubility of poorly soluble drugs do not even represent equivalents, since their choice, preference and applicability would depend *inter alia* on the particular chemical and physicochemical nature of the particular drug substance. Thus, the skilled person would not consider that all the approaches disclosed in general terms in document D15 necessarily form part of the disclosure of the parent application as filed, and

document D15 can only serve as relevant general prior art for the assessment of inventive step.

4.3.10 Similarly, document D43 discloses which are the factors generally known to affect the rate of dissolution of drug dosage forms and classifies then under "three main categories" (page 591): Factors relating to the physicochemical properties of the drug, factors relating to the solid dosage form and effects of compression force on dissolution rate (pages 591 to 594). However, document D43 does not disclose that the approaches classified under different categories are interchangeable, or directly and unambiguously applicable to a particular drug.

4.3.11 Furthermore, none of the prior-art documents cited by the appellant as representing common general knowledge allows the conclusion that the parent application as filed teaches that any conceivable method theoretically known by the skilled person for possibly improving dissolution provides in fact a tablet with the specific active ingredients DRSP and ethinylestradiol providing a rapid dissolution profile of DRSP, irrespective of whether or not the dissolution profile is that actually defined in claim 1 or is a "rapid" dissolution profile obtained following the general recommendations in the general prior art cited (*inter alia* documents D3, D12, D69, D43).

4.3.12 Additionally, the additional technical data and experimental reports D26a, D26b, D45, D46, D46a do not form part of the prior art and are not part of the application documents as filed (either in the parent or in the divisional applications). Therefore, they cannot

be invoked for the assessment of grounds pursuant to Articles 100(c), 123(2) and 76(1) EPC.

4.4 Therefore, for the reasons given above, the main request fails since it extends beyond the content of the earlier application as filed (Article 100(c) EPC in connection with Article 76(1) EPC).

5. *Auxiliary request 1 (Articles 123(2), 76(1) EPC)*

5.1 Claim 1 of auxiliary request 1 differs from claim 1 of the main request basically in that the claim requires that **"drospirenone is provided in a form that promotes rapid dissolution so that** at least 70% of said drospirenone is dissolved from said tablet preparation containing 3 mg drospirenone within 30 minutes, as determined by USP XXIII Paddle Method II using 900 ml water at 37°C as the dissolution media and 50 rpm as the stirring rate" (emphasis added).

The reasoning given for the main request regarding how to apply the principles for assessing added matter in the present appeal case applies *mutatis mutandis* to the auxiliary request.

5.1.1 Explicitly, the application as filed does not disclose physical forms for DRSP promoting rapid dissolution thereof other than those of the embodiments materialised in the second paragraph on page 4.

Therefore, it has to be assessed whether the technical information in claim 1 is implicitly but directly and unambiguously disclosed in the parent application as filed. The parent application as filed neither mentions

nor refers to techniques or approaches generally known in the art for providing physical forms of drugs promoting rapid dissolution. The technical teaching in the parent application as filed relates to two kinds of physical forms for DRSP: micronized, and sprayed onto the surface of inert carrier particles. The fact that the skilled person generally knows from document D15 that there are several alternatives which are theoretically possible for improving the dissolution properties of poorly soluble drugs to be given orally by physical modification of the drug substance (pages 515-519 (Table 1) does not mean that all these possibilities are directly and unambiguously applicable to a particular drug as equivalents. In particular, Table 1 on page 519 mentions "particle size and crystal form modifications" and as options thereto "milling/micronization of drug substance, crystal habit, polymorphic form, solvates, crystal poisoning".

First and foremost, it is not to be assessed whether these are obvious alternatives to be considered by the skilled person when reading the specification of the parent application as filed, but whether these options are necessarily technical information directly and unambiguously derivable from the explicit disclosure of the parent application as filed. However, even after consideration of the common general knowledge reflected in the documents cited by the appellant, such information cannot be regarded as necessarily derivable from the parent application as filed. Document D15 generally teaches on page 515, under the heading "Drug particle size", that: "Erratic bioavailability is a common problem with tablets and capsules containing poorly soluble drugs. With these materials, it has been

found that increasing the available surface area by reducing the particle size can often markedly improve dissolution rates and lead to dramatic improvements in bioavailability." However, the teaching on page 516 in relation to "Crystal form" is not of such general applicability: "Different crystal forms will often exhibit different solubility characteristics and as a consequence of the different external surface areas **or bonding with the crystal lattice**, both the saturation solubility and **the dissolution rate may differ markedly between different crystal forms of the same drug**" (emphasis added). This passage does not teach that in the case of a particular drug substance, DRSP, providing a crystal form would promote rapid dissolution of the substance, or that crystal forms able to promote rapid dissolution of the substance are equivalents for micronization because they behave identically. Document D15 teaches in general terms that there are several approaches which may be contemplated by the skilled person when trying to solve the problem of oral administration of poorly soluble drugs. However, this would be an analysis of obviousness, which is not suitable for the assessment of the disclosed subject-matter within the meaning of Articles 123(2) and 76(1) EPC.

5.1.2 Analogous reasons also apply to the other prior-art documents cited by the appellant, which do not disclose that the different commonly known approaches are interchangeable, or directly and unambiguously applicable to DRSP as equivalents. As a consequence, the skilled person would not necessarily derive from the parent application as filed that such approaches

are implicit alternatives of the physical forms of DRSP explicitly disclosed.

In particular, document D43 teaches in relation to the "effect of the crystalline state of the drug on dissolution" that "the solid phase characteristics of drugs, such as amorphicity, crystallinity, state of hydration and polymorphic structure, have been shown to have a significant influence on the dissolution rate" (page 592, right-hand column).

There is no disclosure whatsoever in the parent application as filed about crystal forms or polymorphs of DRSP, either explicit or implicit. Moreover, the general teaching in the parent application as filed (first paragraph on page 4) does not allow the skilled person to directly and unambiguously understand that theoretically possible crystal forms of DRSP, capable of promoting the dissolution rate of the substance, would ensure the rapid dissolution profile defined in claim 1.

5.1.3 Whether the skilled person would determine the bioavailability of DRSP from the tablets after administration *in vivo* and by using parameters other than the *in vitro* dissolution profile mentioned in the second paragraph on page 4 of the parent application as filed is immaterial for the conclusions reached above.

5.1.4 Therefore, auxiliary request 1 fails since claim 1 contains added matter within the meaning of Articles 123(2) and 76(1) EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald