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Datasheet for the decision of 20 March 2013

Case Number: T 0637/09 - 3.3.02

Application Number: 01900579.2

Publication Number: 1257280

IPC: A61K 31/585, A61P 5/30, A61K 31/565

Language of the proceedings: EN

Title of invention:
Pharmaceutical combination of micronised drospirenone and an estrogen for hormone replacement therapy

Patent Proprietor:
Bayer Pharma Aktiengesellschaft

Opponent:
LABORATORIOS LEON FARMA S.A.

Headword:
Tablet comprising micronised drosperinone and micronised estradiol/BAYER PHARMA

Relevant legal provisions:
EPC Art. 123(2), 56
RPBA Art. 12, 13

Keyword:
"Admission of submissions, documents and claim's requests (point 2)"
"Main request and auxiliary requests I and II (added subject-matter)"
"Auxiliary request IV: inventive step (no)"

Decisions cited:
T 0167/93, T 0007/07, T 1421/05, T 0515/04

Catchword:
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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0637/09 - 3.3.02

D E C I S I O N
of the Technical Board of Appeal 3.3.02
of 20 March 2013

Appellant: (Opponent)
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Decision under appeal:
Interlocutory decision of the Opposition Division of the European Patent Office posted 26 February 2009 concerning maintenance of the European patent No. 1257280 in amended form.

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent No. 1 257 280, based on European patent application No. 01900579.2, which was filed as an international application published as WO 01/52857, was granted with fifty-five claims.

Claim 1 as granted reads as follows:

"1. A pharmaceutical composition in the form of an oral dosage form comprising

i) an estrogen with exception of ethinyl estradiol;
ii) drospirenone in an amount corresponding to a daily dose ranging from 0.25 to 10 mg; and
iii) a pharmaceutically acceptable excipient or carrier,
wherein said drospirenone is in a form having a surface area of more than 10.000 cm^2/g".

Independent claim 2 as granted reads as follows:

"2. A pharmaceutical composition in the form of an oral dosage form comprising
i) an estrogen with the exception of ethinyl estradiol;
ii) drospirenone in an amount corresponding to a daily dose ranging from 0.25 to 10 mg; and
iii) a pharmaceutically acceptable excipient or carrier;
wherein drospirenone is in a form having rapid dissolution such that at least 70% of said drospirenone is dissolved within 30 minutes when the composition is subjected to dissolution testing in 900 ml of water at 37°C using USP XXIII Paddle Method II operated at a stirring rate of 50 rpm".

Independent claim 3 as granted reads as follows:

"3. A pharmaceutical composition in the form of an oral dosage form comprising
i) an estrogen with the exception of ethinyl estradiol;
ii) micronised drospirenone in an amount corresponding to a daily dose ranging from 0.25 to 10 mg; and
iii) a pharmaceutically acceptable excipient or carrier".

II. Opposition was filed and revocation of the patent in its entirety was requested pursuant to Articles 100(b) (lack of sufficiency of disclosure) and 100(a) EPC (lack of inventive step).

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

D1 WO 95/07081
D2 WO 98/27929
D3 WO 01/15701
D4 Fotherby K., Contraception, 1996, 54, 59-69
D5 EP-A-0461290
D6 Chaumeil J.C., Meth. Find. Exp. Clin. Pharmacol., 1998, 20(3), 211-215
D7 McInnes et al, J. Clin. Pharmacol., 1982, 22, 410-417
D8 US 4196188
D9 Maxson et al, Fertility and Sterility, 1985, 44(5), 622-626
D10 Abstract MedLine reference PMID: 8726605
D11 Abstract MedLine reference PMID: 2801843
D14 Nickish et al, Tetrahedron Letters, 1986, 27(45), 5463-5466 and its English translation

D20: D20a, D20b, D20c: *in vitro* dissolution data submitted by the patent proprietor with letter of 20 February 2007

D21 WO 98/06738

D22 Schering data sheet submitted by the patent proprietor with letter of 20 February 2007

D23 Bauer, Frömming and Führer, Pharmazeutische Technologie, 4. Ed. 1993, page 205

D26 Experimental data submitted by the patent proprietor with letter of 20 February 2007 (pharmacokinetic data)

D27 Garrett et al, J. Pharmaceutical Sciences, 1971, 60(12), 1801-1809

D28 Pramar et al, J. Pharmaceutical Sciences, 1991, 80(6), 551-553

D30 Hargrove et al., Am J Obster Gynecol, 1989, 161(4), 948-951

D31 Decision of 3 March 2008, United States District Court of New Jersey, Civil Action No. 05-cv-2308 (PGS)

D32 Aulton M.E., Pharmaceutics: The Science of Dosage Form Design, 1988, chapters 1 and 9

D33 Krause et al, J. Chromatography, 1982, 230, 37-45

D34 Krause et al, Steroids, 1982, 40(1), 81-90

D35 Krause et al, European J. Clin. Pharmacol., 1983, 25, 231-236

D38 WO 2005/087194

D39 Yasmin^{R} Product Monograph

D40 Decision of 5 August 2009, US Court of Appeals for the Federal Circuit 2008-1282 (CAFC decision relating to US6787531)

D41 McLachlan et al, Br J clin Pharmac 1993, 36, 405-411

D42 Chenet et al, Pharm. Res., 2008, 25(1), 123-134

D43 Kondo et al, Biopharmaceutics & Drug Disposition, 2003, 24, 45-51

D45 Melia et al, Aliment. Pharmacol. Therap., 1989, 3, 513-525

D46 Experimental data (working report No. A01499) submitted by the patent proprietor with letter of 4 October 2012

D47 Experimental data (working report No. A01500) submitted by the patent proprietor with letter of 4 October 2012

D48 Transcript from FDA's homepage about Yasmin^{R}

D49 Copy of a letter from FDA to Berlex

D50 Information page for Yasmin^{R}

D51 Ellman's declaration of 28 November 2003

D52 Copy of "Informed consent" form

D53 Pages 1, 3 and 28 of the transcript from Mr Ellman's cross-examination

D54 Copy of "Patient information" leaflet

D55 Copy of "Instructions for use"

D56 Berlex Case report

D57 Cohen et al, Pharm. Res., 1990, 7(10), 983-987

D58 Copy of decision T 0007/07 of 7 July 2011

D59 copy of an opposition division decision dated 30 January 2012 (filed by the opponent with letter of 4 October 2012 as document D46)

D60 copy of an opposition division decision dated 29 March 2012 filed by the opponent with letter of 4 October 2012 as document D47

D61 WO 2006/015956 filed by the opponent with letter of 4 October 2012 as document D48

D62 Rudolf Voigt, Lehrbuch des pharmazeutischen Technologie, 6. Edition, 1987, 470-474

D64 Paul Heinz List, Arzneiformlehre, 4. Edition, 1985, 529-530

D65 PubMed abstract, Moschchak et al, Am. J. Obstet. Gynecol., 1982, 144(5), 511-518
D66 "Acta de acuerdos del consejo de administración de laboratorios León Farma, S.A., Sociedad Unipersonal." filed by fax at the oral proceedings on 4 December 2012
D67 Certificate in English language by Ms I. Alcalde Giraudo dated 4 December 2012, filed by fax at the oral proceedings on the same date; "Escritura de renovación de cargos "*Laboratorios León Farma S.A.*"" with several annexes in Spanish
D68 Authorisation of Mr Schön as representative for the appellant filed by fax at the oral proceedings on 4 December 2012 (2 pages)

IV. The present appeal lies from an interlocutory decision of the opposition division maintaining the patent in amended form on the basis of the main request filed with the letter of 9 October 2008 (Article 101(3)(a) EPC).

The main request filed with the letter of 9 October 2008 contained forty-six claims. Claim 1 read as follows:

"1. A pharmaceutical composition in the form of an oral dosage form comprising
i) an estrogen with the exception of ethinyl estradiol;
ii) drospirenone in an amount corresponding to a daily dose ranging **from 0.25 to 4 mg**;
and
iii) a pharmaceutically acceptable excipient or carrier,
wherein said drospirenone is in a form having a surface area of more than 10,000 cm^2/g,

and **wherein said estrogen is in micronised form or sprayed from a solution onto the surface of inert carrier particles**". (emphasis added)

Independent claim 2 read as follows:

"2. A pharmaceutical composition in the form of an oral dosage form comprising
i) an estrogen with the exception of ethinyl estradiol;
ii) drospirenone in an amount corresponding to a daily dose ranging **from 0.25 to 4 mg**;
and
iii) a pharmaceutically acceptable excipient or carrier,
wherein drospirenone is in a form having rapid dissolution such that at least 70% of said drospirenone is dissolved within 30 minutes when the composition is subjected to dissolution testing in 900 ml of water at 37°C using USP XXIII Paddle Method II operated at a stirring rate of 50 rpm, **and wherein said estrogen is in micronised form or sprayed from a solution onto the surface of inert carrier particles**". (emphasis added)

Independent claim 3 read as follows:

"3. A pharmaceutical composition in the form of an oral dosage form comprising
i) an estrogen with the exception of ethinyl estradiol;
ii) micronised drospirenone in an amount corresponding to a daily dose ranging **from 0.25 to 4 mg**;
and
iii) a pharmaceutically acceptable excipient or carrier,
wherein said estrogen is in micronised form or sprayed from a solution onto the surface of inert carrier particles". (emphasis added)

V. The opposition division held that the amendments introduced met the requirements of Rule 80 EPC. Moreover, the opposition division found that the main request met the requirements of Article 123(2) EPC.

As regards the ground of opposition under Article 100(b) EPC, the opposition division considered that the patent in suit contained sufficient technical information for the skilled person to prepare the compositions claimed in claim 2 and that the subject-matter claimed in claims 2, 15 and 28 fulfilled the requirements of Article 83 EPC since.

The opposition division was of the opinion that the subject-matter claimed in the main request was novel. Furthermore, the opposition division considered that the "*subject-matter of claims 1-46 involved an inventive step (Article 56 EPC)*". In particular, the opposition division was of the opinion that documents D1 and/or D2 represented the closest prior art. The opposition division defined the problem to be solved as the provision of a pharmaceutical composition comprising drospirenone with improved bioavailability. In the opposition division's view, the solution was to provide drospirenone "*in a form having rapid dissolution, e.g. micronised form*".

The opposition division considered that the "*subject-matter of claims 1 to 46*" involved an inventive step (Article 56 EPC).

VI. The opponent (appellant) filed an appeal to the opposition division's decision. The appellant filed

with its grounds of appeal two further documents, namely D38 and D39.

VII. The appellant filed with a letter dated 25 September 2009 a copy of a decision of the US Court of Appeals for the Federal Circuit (D40).

VIII. The patent proprietor (respondent) filed a reply to the grounds of appeal (letter dated 21 December 2009). It filed therewith three further documents D41 to D43 and a document D44 concerning CAFC judges.

IX. The appellant filed with a letter dated 25 May 2010 a reply to the respondent's arguments.

X. The respondent filed a letter dated 21 February 2011 with further counter-arguments contesting the appeal.

XI. The appellant filed a further letter dated 8 April 2011 in which it cited the appeal case T 7/07 (same board in another composition) concerning the patent EP-B1-1214076, which derives from the application WO 01/15701 (document D3).

XII. A summons to oral proceedings to be held on 4 December 2012 was sent to the parties on 11 June 2012. A board's communication pursuant to Article 15(1) RPBA expressing the preliminary opinion of the board was sent to the parties as an annex to the summons. In said communication the parties' attention was drawn *inter alia* to the fact that the set of claims of the main request filed with the letter of 9 October 2008 contained several independent claims (claims 1, 2, 3, 14, 15, 16, 27, 28, 29) which were characterised by

different technical features. Thus, the parties were informed that the subject-matter of the independent claims required a separate analysis.

XIII. The appellant filed a letter dated 4 October 2012 with further submissions. It submitted *inter alia* (see point 6, "Yasmin^{R} - Prior use") that in decision T 7/07 it had been decided that the product Yasmin^{R} was publicly available before 31 August 1999 (effective filing date of EP-B1-1214076). It had thus been publicly available before the priority date (18 January 2000) of the patent contested in the present appeal. In the appellant's view, said knowledge formed part of the prior art for the assessment of inventive step (Articles 54(2) and 56 EPC). It filed several documents as annexes to its letter (D58 to D61, as renumbered with the appellant's letter dated 2 November 2012). Moreover, with said letter the appellant raised objections within the meaning of Article 123(2) EPC against the set of claims serving as the basis for the opposition division's decision.

XIV. The respondent filed a letter dated 4 October 2012 with further submissions and arguments. As an annex thereto it filed documents D45 to D57. It also filed a new main request and two auxiliary requests (auxiliary request I and II), as a working copy and as a clean copy.

Claim 1 of the main request reads as follows:

"1. A tablet comprising
i) 1 mg estradiol;
ii) 2 mg drospirenone; and
iii) a pharmaceutically acceptable carrier,

wherein drospirenone is in a form having rapid dissolution such that at least 70% of said drospirenone is dissolved within 30 minutes when the tablet is subjected to dissolution testing in 900 ml of water at 37°C using USP XXIII Paddle Method II operated at a stirring rate of 50 rpm, and wherein estradiol is in micronised form or sprayed from a solution onto the surface of inert carrier particles."

Independent claim 2 of the main request reads as follows:

"2. A tablet comprising
i) 1 mg estradiol;
ii) 2 mg micronised drospirenone; and
iii) a pharmaceutically acceptable excipient or carrier,
wherein estradiol is in micronised form or sprayed from a solution onto the surface of inert carrier particles."

Claim 1 of auxiliary request I reads as follows:

"1. A tablet comprising
i) 1 mg estradiol;
ii) 2 mg drospirenone; and
iii) a pharmaceutically acceptable carrier,
wherein drospirenone is in a form having rapid dissolution such that at least 70% of said drospirenone is dissolved within 30 minutes when **a tablet preparation containing 3 mg of drospirenone** is subjected to dissolution testing in 900 ml of water at 37°C using USP XXIII Paddle Method II operated at a stirring rate of 50 rpm, and wherein estradiol is in

micronised form or sprayed from a solution onto the surface of inert carrier particles." (emphasis added)

Independent claim 2 of auxiliary request I is identical to claim 2 of the main request.

Auxiliary request II contains a single claim which is identical to claim 2 of the main request and auxiliary request I.

XV. The appellant filed a letter dated 2 November 2012 in which it renumbered the documents it had filed with its letter of 4 October 2012 as D58 to D61. It also filed arguments in relation to the respondent's requests filed with the letter of 4 October 2012, in particular in relation to Articles 123(2) and 84 EPC. It further submitted arguments in relation to the grounds pursuant to Article 100(b) EPC and the assessment of inventive step (Article 56 EPC). Moreover, it requested that documents D45 to D57 (filed with the respondent's letter of 4 October 2012) not be admitted into the proceedings. An authorisation for Mr Schön as a further representative for the appellant, which was signed by Ms Alcalde and Mr Seco, was also filed with said letter.

XVI. The respondent filed with a letter dated 8 November 2012 counter-arguments in relation to the issue of added matter (Article 123(2) EPC). In particular, it submitted that the ground of opposition pursuant to Article 100(c) EPC was not within the framework of the present appeal proceedings. It therefore requested that the objections within the meaning of Article 123(2) EPC not be admitted. It also filed counterarguments in relation to Articles 83 and 56 EPC. Moreover, it filed

a further document, namely D62. The respondent objected to the admission of the appellant's late-filed objection which concerned the prior use in decision T 7/07 as prior art for the assessment of inventive step in the present appeal case. Moreover, the appellant also requested remittal to the department of first instance if such an objection were to be admitted.

XVII. With a letter dated 15 November 2012 observations by a third party under Article 115 EPC were filed. Two documents, namely D64 and D65 were attached thereto.

XVIII. With a letter dated 3 December 2012, filed by fax, the respondent made it clear that it had not abandoned the previous main request, i.e. the set of claims as maintained by the opposition division, which constituted its third auxiliary request. With said letter it filed a copy of said set of claims.

XIX. Oral proceedings took place on 4 December 2012. At 21.45 hrs, the chairman declared the oral proceedings adjourned. He informed the parties that the board would send an invitation for continuation of the oral proceedings.

During the oral proceedings on 4 December 2012 the respondent withdrew its third auxiliary request filed with the letter dated 3 December 2012 and filed a new auxiliary request III and an auxiliary request IV.

Auxiliary request III filed at the oral proceedings on 4 December 2012 contained only one single claim, which differed from claim 1 of the main request filed with the letter of 4 October 2012 in that the expression "or

sprayed from a solution onto the surface of inert carrier particles" was deleted at the end of the claim.

Auxiliary request IV filed at the oral proceedings on 4 December 2012 contained a single claim only, which differed from claim 1 of the auxiliary request II filed with the letter of 4 October 2012 in that the expression "or sprayed from a solution onto the surface of inert carrier particles" at the end of the claim had been deleted.

XX. Summons to oral proceedings to be held on 20 March 2012 were sent to the parties on 11 December 2012.

XXI. The minutes of the oral proceedings of 4 December 2012 were sent to the parties on 17 December 2012.

XXII. The appellant filed a letter dated 19 February 2013 with objections under Articles 83 and 56 EPC against the subject-matter of claim 1 of auxiliary request IV.

XXIII. Third-party observations under Article 115 EPC were filed with a letter dated 20 February 2013, which was signed by Mr Kindler of Hoffmann and Eitle. Several documents were filed as annexes to said letter.

XXIV. The respondent filed a letter dated 4 March 2013. It contested the admission of the appellant's letter dated 19 February 2013 and of the third-party observations dated 20 February 2013. It requested that the board inform the parties whether it intended to admit the appellant's letter dated 19 February 2013 and the third-party observations dated 20 February 2013.

XXV. Oral proceedings were resumed on 20 March 2013.

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

(a) During the oral proceedings on 4 December 2012 the appellant filed by fax documents D66 to D68 by way of reply to the respondent's objections in relation to the authorisation of Mr Schön filed with the letter of 2 November 2012.

(b) The main request and auxiliary requests I and II filed with the respondent's letter of 4 October 2012 should not be admitted into the proceedings since they created problems under Article 123(2) EPC and the patentee had not provided any proper justification for their filing.

Moreover, the appellant denied that it had ever agreed to the allowability of amendments under Article 123(2) EPC. Additionally, the board had both the duty and the power of the board of appeal to substantively review the first-instance decision. The opposition division had concluded on Article 123(2) EPC and thus the board had both the duty and the power to revise the amended claims under Article 123(2) EPC. Furthermore, Article 123(2) EPC was within the framework of the present appeal since the respondent had filed amended claims.

(c) Documents D64 and D65 should be admitted into the proceedings since they were highly relevant. The submissions in the third-party observations under Article 115 EPC dated 15 November 2012 concerned

objections already in the proceedings and should therefore be admitted.

(d) The appellant submitted that the third-party observations under Article 115 EPC dated 20 February 2013 should be admitted into the proceedings since the debate had not been closed at the oral proceedings on 4 December 2013 in relation to the issues concerning Articles 56 and 83 EPC. The respondent could not have been surprised by the observations since the issues commented on by the third party had been under discussion during the present appeal proceedings and formed part of their framework.

(e) The objection of lack of inventive step relying on public prior use in accordance with the findings of decision T 7/07 should be admitted into the appeal proceedings since it was a highly relevant prior use. The inventive step objection concerned document D1 together with the prior use.

The appellant further submitted that documents D48 to D56 filed by the respondent should not be admitted into the proceedings since they did not provide anything relevant contrary to findings in decision T 7/07 in relation to the prior use.

(f) Documents D45 and D57 should not be admitted since they did not add anything which was *prima facie* relevant. In relation to documents D46 and D47, the additional data were not relevant. As regards document D62, it related to general knowledge which did not appear to be particularly relevant for the present case.

By way of reply to the submissions in the context of the respondent's request for admission of documents D45, D46, D47, D57 and D62, the appellant argued that Article 83 EPC was within the framework of the appeal proceedings since the first instance decision had to undergo a review by the board. Moreover, new amended claims had been filed in appeal proceedings.

(g) Documents D59 and D60 should be admitted since the opposition division's decisions concerned similar issues.

(h) *Allowability of the main request and auxiliary requests I and II filed with the letter of 4 October 2012 under Article 123(2) EPC*

The appellant submitted that claim 1 of the main request originated from claims 1, 5, 6, 7 and 8 of the application as filed. The additional features in claim 1 (tablet, specific amounts, specific dissolution profile, specific form for estradiol) concerned a combination of features which was not disclosed in the application as filed. Said features were disclosed separately in the application as filed: tablets were disclosed on page 15, lines 19 to 24 of the application as filed, specific amounts for estradiol in combination with specific amounts for drospirenone (DRSP) were disclosed on page 12, lines 26 to 30 of the application as filed, and the form of the estrogen as micronised or sprayed from a solution onto the surface of inert carrier particles appeared on page 8, lines 13 to 14 and 16 of the application as filed. Moreover, a "rapid dissolution" profile for drospirenone was defined on page 7, lines 28 to 32 of the application as filed but

only in connection with a tablet preparation containing 3 mg of drospirenone. The "rapid dissolution" profile on page 7 of the application as filed only addressed micronised forms.
The amended claims did not concern combinations of granted claims. Therefore, the assessment of Article 123(2) EPC could not be restricted by claiming that Article 100(c) EPC was not within the framework of the present appeal. The feature concerning the dissolution profile was defined differently in the amended claims of the main request from the way it was in claim 2 as granted. Therefore, the features had to be assessed in their new context.

Additionally, the appellant argued that pages 7 and 8 of the application as filed referred to two different dissolution profiles: *in vitro* and *in vivo*. The prior art documents cited by the respondent did not add anything in favour of the allowability of the amended claims. Document D45, Table 1 merely referred to means to improve dissolution. The dissolution profile disclosed in document D57, Table 1 was not identical to that appearing on page 7 of the application as filed. The appellant contested the respondent's allegation that the dissolution profile defined on page 7 of the application as filed applied to any other tablet since the application as filed disclosed amounts of DRSP up to 10 mg. Therefore, it was not possible to conclude that the profile given on page 7 for a 3 mg tablet was of general applicability to any tablet independent from the amount of DRSP. Moreover, the dissolution rate was influenced by the choice of carriers and excipients (application as filed, page 8, last paragraph). The appellant also submitted that claim 1 of the main

request related to an artificial combination of features from the application as filed and that the application as filed did not disclose tablets as a preferred embodiment. Other dosage forms were disclosed. In particular, the examples also related to oral solutions (example 2). The disclosure in the application as filed concerning the drug or drugs being sprayed onto the surface of inert carrier particles did not necessarily refer to tablets.

The appellant further submitted that claim 2 of the main request contravened the requirements of Article 123(2) EPC for analogous reasons to those given for claim 1 of the main request. The claim related to an artificial combination of features which represented an unallowable intermediate generalisation.

The appellant maintained its arguments in relation to claim 2 of auxiliary request I, which is identical to claim 2 of the main request. It also stated that its arguments in relation to claim 1 of the main request applied *mutatis mutandis* to claim 1 of auxiliary request I, which merely differed therefrom in the specification of a 3 mg tablet in the dissolution profile.

(i) *Admission of auxiliary requests III and IV filed at the oral proceedings on 4 October 2012*

The appellant objected to the admission of the late-filed auxiliary requests III and IV since they were not clearly allowable under Article 123(2) EPC.

(j) *Auxiliary request IV (Articles 123(2) and 56 EPC)*

The appellant argued that claim 1 of auxiliary request IV contravened the requirements of Article 123(2) EPC for analogous reasons to those submitted in relation to claim 2 of the main request. The subject-matter claimed resulted from an unallowable combination of features.

As regards the inventive step issue (Article 56 EPC) the appellant submitted the following:

Document D1 represented the closest prior art. The difference over the prior art was that DRSP was micronised. If the problem to be solved was to increase the bioavailability of DRSP then it had to be said that the patent in suit did not provide any data in this respect. The appellant argued that an effect serving as the basis for the definition of the problem to be solved should not be based on post-published evidence or documents. Moreover, document D26 related to post-published evidence submitted by the patentee, but the actual constitution of the tested dosage form was unknown. The bioavailability which was determined in post-published document D3, example 4 concerned an oral administration of a microcrystalline suspension containing 3.13 mf DRSP and was thus not relevant. The appellant stressed that claim 1 of auxiliary request IV was not restricted to any particular "rapid dissolution" profile and that the claim did not even require that the tablet provides a rapid dissolution. Therefore, the problem to be solved had to be redefined so as to provide an alternative pharmaceutical form. The solution to the problem was that DRSP was micronized, since it was already known from document D4

(pages 61, 62) that to micronise estradiol improved absorption of the drug, which was generally known for its poor absorption.

The appellant also cited the review article D45, page 515, last paragraph, in which particle size reduction was taught as being commonly employed as one of the simplest ways to increase the absorption rates of poorly soluble drugs from tablets and capsules. It also cited the US district court decision D31, paragraph bridging pages 11 and 12, in which micronisation had been acknowledged as a commonly used technique for increasing the bioavailability of orally administered drugs, and US Court of Appeal decision D40, page 3, first paragraph, in which it had been acknowledged that all commercially available oral contraceptives used micronised progestins and/or estrogens. The respondent's reply dated 21 February 2011, point 2, did not give convincing arguments why the skilled person would not apply this generally acknowledged teaching to DRSP. Document D4, pages 61, 62 addressed the micronisation of estradiol and page 65, left column, last paragraph taught that, like estradiol, the absorption of progesterone can be improved by micronisation. Document D7 confirmed that micronization was a valid technique for enhancing *in vitro* dissolution, as well as the bioavailability of spironolactone, a synthetic steroid which had an acid sensitive lactone group. The appellant also cited document D6, which related to micronisation as a method of improving the bioavailability of poorly soluble drugs, in which micronised spironolactone was explicitly mentioned (page 213, right-hand column).

Starting from document D1, the object was to modify the bioavailability of the drugs, and it was obvious to provide the drugs in micronised form. There was no prejudice in the prior art against doing so with DSPR. The appellant cited the Handbook D32, page 8, in particular the second paragraph under the heading "*Particle size and surface area*", in which it was taught that it was generally recognized that poorly soluble drugs showing a dissolution rate-limiting step in the absorption process are more readily bioavailable when administered in a finely subdivided form.

Additionally, the appellant submitted that the Krause articles D33 to D35 provided the skilled person with further motivation to micronise DRSP. The appellant pointed to the structural similarities between spirorenone and drospirenone (DRSP), which was 1,2-dihydrospirorenone, a metabolite of spirorenone (document D33, abstract and Figure 1). In particular, the lactone configuration and its spatial surroundings were comparable. In both compounds the lactone ring was subject to acid-catalyzed rearrangement, as shown from *in vitro* studies (D33, page 41). However, document D33 taught that the process of rearrangement was relatively slow compared with possible absorption rates in the stomach (page 41). Additionally, document D33 also taught, as a result of the investigation of the possible appearance in blood of the non-active acid-catalysed rearrangement product of spirorenone which might have been formed in the stomach, that the lactone rearrangement product of spirorenone was not detectable in plasma (limit of detection was less than 5 ng/ml), indicating that the absorption process was much faster than the acid-catalysed isomerisation of the drug. The

skilled person would not have expected relevant differences for DRSP. Figure 4 in document D33 (page 42) merely showed that the acid-catalysed rearrangement of DRSP went a bit faster than the acid-catalysed rearrangement of spirorenone.

The appellant disputed the respondent's interpretation of the content of document D33. In particular, Table II in document D33 (page 43) showed absorption $t_{1/2}$ of 1/2 h for spirorenone. The results in Table II and Figure 5 in D33 had to be understood in the light of the experimental conditions stated on page 38 (blood samples were taken at 0, 0.5, 1, 1.5, 2, … hours). The experiment performed in D41 was different.
Document D35 confirmed that there was no problem of clinical relevance with the acid-catalysed isomerisation (page 231, right-hand column, second paragraph). Moreover, document D35 (page 235, right-hand column, first paragraph) suggested that any potential problem relating to an incomplete absorption of higher doses of spirorenone could be solved using different galenic formulations and by using micronised materials, as had been the case with spironolactone. Thus, the prior art did not deter the skilled person from the micronisation of the drug. On the contrary, micronisation was suggested if any problem concerning absorption was detected. Moreover, in document D34 a microcrystalline suspension containing 2 mg of spirorenone was administered. The skilled person would have understood that a macrocrystalline spirorenone had been micronised. In this context the appellant cited document D3, page 3, lines 21 to 23, page 12, example 2, page 11, example 1 and page 20, example 4. The appellant submitted that the prior art documents did

not show any prejudice against using micronised DRSP and did not lead the skilled person away from choosing micronisation as a solution to the problem to be solved.

The appellant also submitted that claim 1 covered any kind of tablet. Therefore, enteric coated tablets or tablets in which the drug was embedded in a matrix were not excluded from the claim's wording. Thus, it had to be investigated whether the problem defined by the respondent had actually been solved within the whole scope claimed and what the solution was that was proposed by the claimed subject-matter. As regards the post-published evidence D26, the respondent had not provided full and complete information about the undertaken tests. Thus, the depicted results could not be used in support of inventive step. In relation to the post-published evidence in document D3, it was not sufficient to support an alleged "improved bioavailability" for the whole scope claimed.

The appellant also argued that spironolactone was acid-sensitive and less stable at acid pH than at neutral pH (document D28, page 551, second paragraph, under the heading "Results and Discussion") and that document D35 taught that it had been micronised to improve its absorption. The appellant argued that the presence of a 15, 16-methylene group did not always increase the acid sensitivity of the spirolactone ring since document D14 showed that a 15α, 16α-methylene spirolactone derivative was not acid labile. Moreover, the rearrangement experiments in document D14 concerned *in vitro* experiments. It was the *in vivo* behaviour as shown in document D33 which was relevant for the skilled person. The inactive isomer had not been

detected *in vivo*. Document D33 taught the skilled person that isomerisation *in vivo* was slow in comparison with absorption. Documents D33 to D35 further taught the skilled person to micronise DRSP in order to improve absorption and that there was absorption already in the stomach.

Documents D4 to D11 pointed to micronisation as the solution to the technical problem actually solved. The experimental results displayed in document D20a could not be used in support of the presence of an inventive step since there was a lack of information concerning the tested formulations and the test conditions.

The acid sensitivity of a drug was a matter of degree. Document D32 recommended enteric coating of tablets for acid-instable drugs such as penicillin or erythromycin (page 161, right-hand column). However, the acid instability of these two antibiotic drugs was much higher than the relative acid sensitivity of the steroids with the spirolactone ring, as a result of the extreme differences in chemical structure and polarity. In the appellant's view DRSP and spirorenone bore a weak acid group and document D32 taught that weak acidic drugs can be absorbed in the stomach. Moreover, unionised drugs were more likely to be absorbed faster in the stomach (D32, page 145, right-hand column). Document D32 showed very clearly that there was drug absorption from the stomach (page 136, Figure 9.1). To know with certainty whether or not DRSP was actually absorbed from the stomach and to what extent would have required *in vivo* experimentation, which did not form part of the knowledge disclosed in the prior art.

However, the knowledge of a certain acid sensitivity of DRSP would not have deterred the skilled person from its micronisation, since the *in vivo* pharmacokinetic tests for spirorenone had shown that a similar acid sensitivity had not caused any problems of clinical relevance. Moreover, document D32 disclosed that gastric fluid exhibited a pH within the range 1 to 3.5, and that the pH increased with food ingestion. The respondent argued that the closer the pH to 3.5 the lesser the degree of isomerisation of DRSP, as could be seen from document D22 (DRSP stable at pH 4).

Document D1 mentioned that the preparations for oral administration of estrogens and progestogens comprise the drugs in common form (page 4, lines 24, 25). Thus, micronisation of the drugs was not excluded. Document D4 taught to micronise estrogens and progestogens.

Additionally, the appellant stressed that claim 1 of auxiliary request IV was not restricted to a tablet having a particular dissolution profile. The appellant also submitted that the claim even encompassed enteric coated tablets or tablets in which the drugs were embedded in a matrix.
The appellant argued that there were limits to the interpretation of claims in the light of the description. It cited board of appeal decisions T 1018/02 of 9 December 2003 and T 1208/97 of 3 November 2000 (point 4).
Claim 1 of auxiliary request IV encompassed any kind of tablet. Additionally, enteric coated tablets were discussed in decision D31 (page 15) as having a large inter-subject variability. This aspect was confirmed by document D32, page 146, right-hand column.

Therefore, the problem to be solved could not be identified as providing an improvement but could only be defined as providing alternative tablets. The proposed solution, which concerned micronisation of the drugs, was obvious.

The appellant also contested the respondent's allegation that the tablets claimed had a rapid dissolution profile as a direct result from the drugs being micronised, since neither the actual size of the particles nor the nature and form of the other constituents in the tablets (excipients, carriers, coating) had been specified in the claim. The appellant argued that the definition given on page 7, lines 23 to 28 of the application as filed, which referred to several size constraints made in relation to 2 or to 20 particles, respectively, in a batch of 200 mg substance could not serve to delimit the claimed tablet which contained 2 mg of micronised DRSP. The documents cited by the respondent in relation to particle sizes disclosed different sizes (defined by means of different parameters) which varied from one to another. In particular, document D6 on page 213 disclosed a median particle size of 3 micrometers for griseofulvin, but document D6 also disclosed micronisation as a method for reducing particle size that did not produce a powder with a uniform particle size: coarse, intermediate and fine particles could be obtained (page 212).

Furthermore, document D4, page 62, left-hand column (second full paragraph) showed how the pharmacokinetic profile (t_{max} and C_{max}) was dependent on particle size. The experimental data provided by the respondent were silent in relation to the actual particle size for the micronised DRSP used. Moreover, document D4 showed that

even if a particular micronisation improved absorption for estradiol it did not necessarily lead to improved therapeutic effect.

In response to the respondent's final comments to disregard documents D1 and D2 as being unrelated and remote, the appellant stated that the claimed tablets were not restricted by the use as HRT. Therefore documents D1 and D2 would both be considered by the skilled person. They disclosed the combination DRSP together with estradiol.

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

(a) The respondent contested at the oral proceedings on 4 December 2012 the authorisation of Mr Schön filed with the letter dated 2 November 2012. In particular, it questioned whether the undersigned persons in the document filed with the letter of 2 November 2012 were authorised to sign the authorisation since their position in relation to the opponent's company had not been declared.

(b) The respondent submitted that the discussion on the admission of the sets of amended claims filed with its letter dated 4 October 2012 (main request and auxiliary requests I and II) depended on whether further objections regarding added matter would be allowed by the board. The respondent argued that the discussion of added subject-matter had to be restricted to amendments going beyond the subject-matter which had been maintained by the opposition division and that only the features which were not explicitly mentioned in the

granted claims could be investigated. Article 100(c) EPC was not a ground of opposition in the present case and the patentee did not give consent to its introduction in appeal proceedings. It cited Enlarged Board of Appeal decisions G 9/91, OJ EPO 1993, 408 and G 10/91, OJ EPO, 1993, 420.

The main request and auxiliary requests I and II had been filed with the letter of 4 October 2012 as a precautionary measure to prevent objections under Article 123(2) EPC. As a matter of fact, the appellant had raised objections under Article 123(2) EPC with its letter dated 4 October 2012 although it had not raised any such objections with its grounds of appeal. In this context it cited Article 12(4) RPBA and decision T 1421/05 of 18 January 2011.

It also cited board of appeal decisions T 1002/92 of 6 July 1994 and T 515/04 of 5 October 2006. In particular, it quoted point 4.3 of decision T 515/04: "*an objection under Article 123(2) EPC is not allowable if it is raised for the first time at the appeal stage and does not arise from an amended part of the claim. It is thus not allowable if it arises from a granted claim or a feature already present in the granted claims which was neither challenged in the Notice of Opposition under Article 100(c) EPC nor examined by the Opposition Division on its own motion*". In the present case, the objections within the meaning of Article 123(2) EPC did not arise from amendments introduced in opposition and appeal proceedings, but concerned features already present in the granted claims. Therefore they should not be allowed in appeal proceedings.

The respondent further argued that the filing of the main request and auxiliary requests I and II was made as a reply to the respondent's objections submitted in the appeal proceedings. They had been filed two months before the oral proceedings of 4 December 2012. Thus, the appellant had had enough time to react. Moreover, since the requests concerned the deletion of claims in order to simplify the case, and in view of the fact that the introduced amendments were easy to handle the amended sets of claims filed with the letter of 4 October 2012 should be admitted into the proceedings. The amendments had been introduced in order to pre-empt objections within the meaning of Articles 123(2) and 84 EPC.

(c) The respondent contested the admission of the third-party observations under Article 115 EPC filed with a letter dated 15 November 2012 and the admission of documents D64 and D65. The third party was not a party to the appeal proceedings and the observations had been filed too late. The late-filed documents would not have been admitted even if they had been filed by a party to the proceedings.

(d) Furthermore, the third-party observations under Article 115 EPC dated 20 February 2013 and the annexes thereto should not be admitted into the proceedings either. These observations had been filed after the oral proceedings on 4 December 2012 were adjourned and a date for continuation of the oral proceedings scheduled for the 20 March 2013. The board had not decided at the end of the oral proceedings on 4 December 2012 to continue the proceedings in writing

but to adjourn the oral proceedings. The third party under Article 115 EPC was not a party to the appeal proceedings. Thus, the third party under Article 115 EPC should not be allowed to intervene during the course of oral proceedings. The letter dated 20 February 2013 contained *inter alia* comments about the oral proceedings of 4 December 2012 and observations which, if admitted, would allow the third party to actively participate in the discussions during the oral proceedings. This would be contrary to the spirit of Article 115, last sentence and Article 107 EPC. Even if the board considered that the present appeal proceedings were to be continued in writing after the oral proceedings on 4 December 2012, there was no justification for such an abusive late-filing of observations by a third party. Moreover, if the third-party observations did not suppose a change to the discussion forming already part of the appeal, the third party should have filed its observations earlier.

(e) The respondent submitted that the objection of lack of inventive step relying on public prior use in accordance with the findings of decision T 7/07 should not be admitted into the appeal proceedings since this was an inadmissible change of the appellant's case. Decision T 7/07 had been available for one year, but the appellant raised the objection of lack of inventive step in relation to decision T 7/07 for the first time with its letter of 4 October 2012.

The respondent argued that documents D48 to D56 filed with its letter of 4 October 2012 should be admitted into the proceedings if the change in the appellant's case in relation to the prior use in decision T 7/07

were to be found admissible. These documents had not been available to the board in case T 7/07 and they might change the board's view in relation to the findings of prior use.

(f) The respondent requested that documents D45, D46, D47, D57 and D62 be admitted into the proceedings, since if the board considered that Article 83 EPC was within the framework of the appeal proceedings they would be highly relevant. The respondent further argued that Article 83 EPC was within the framework of the appeal proceedings only in so far as the amendments introduced into the claims during the appeal proceedings were concerned, since the findings of the opposition division regarding Article 100(b) EPC had not been challenged in the statement of grounds of appeal.

(g) The respondent objected to the admission of documents D59 to D60. It argued that these documents were decisions of opposition divisions in allegedly similar cases which were not relevant since they were first-instance decisions taken on the basis of different facts. D61 was a post-published document and it was irrelevant for the present appeal proceedings.

(h) *Allowability of the main request and auxiliary requests I and II filed with the letter of 4 October 2012 under Article 123(2) EPC*

The respondent stated that, since Article 100(c) EPC was not within the framework of the present appeal, only amendments introduced in the granted claims were to be investigated. Claim 1 of the main request

originated from claim 2 as granted and from claim 2 of the set of claims as maintained by the opposition division. It also referred to claims 5, 7, 8 and 9 as granted in relation to the specification of estradiol as the estrogen drug and of the micronised form. The specification of the dosage form as tablet also appeared on page 7 of the application as filed in connection with the dissolution profile. The respondent argued that the claims had to be read by the skilled person and that a mere semantic approach should be avoided. In the amended claims the skilled person (a pharmaceutical chemist working in pharmaceutical dosage forms) was presented with information which was directly and unambiguously derivable from the application as filed. The "rapid dissolution" was disclosed in generic terms on page 7, lines 17 to 19 of the application as filed. The "rapid dissolution" profile on page 7, lines 28 to 32 of the application as filed was generally applicable and not restricted to micronised drospirenone. It also addressed the alternative in which drospirenone was sprayed onto the surface of an inert carrier. The paragraph on page 8, lines 4 to 9 of the application as filed, which referred to the dissolution rate of drospirenone, concerned the general teaching and the crux of the invention. In this context the respondent referred to document D45 (pages 518, 519, Table 1) as a review article for dissolution rates, which showed that there were different techniques for achieving rapid dissolution profiles, and to document D57 (page 985, left-hand column, table 1), which showed that the definition of the dissolution profile was a standard definition for dosage forms. The respondent further submitted that the "rapid dissolution" profile defined

on page 7 of the application as filed did not apply only to tablets containing 3 mg drospirenone. The claimed tablet also attained that dissolution profile since it contained a smaller amount of DRSP, i.e. 2 mg. It also referred to the experimental data D46 and D47. Moreover, the last paragraph on page 8 of the application as filed merely mentioned that carriers or excipients might be used which could make an even better dissolution profile. The respondent also pointed to page 9, lines 19 to 21 and page 12, lines 27 to 30 and to the examples as the basis for the choice of the dose of 1 mg estradiol and 2 mg DRSP (drospirenone) as a preferred combination. Moreover, the respondent argued that tablets were individualised as preferred embodiments on page 15, lines 9 to 24 and in the examples, in particular example 1. The solutions in example 2 were disclosed as reference solutions.

The respondent cited decision T 343/90 of 26 May 1992, point 2.2 of the reasons and stressed that a literal interpretation of the application was inappropriate, since the addressee of any technical information is the notional person skilled in the art, who would not stick to the wording, but would consider the content of any document in the light of his general knowledge in the technical field. The respondent quoted decision T 296/96 of 12 January 2000, point 3.1 of the reasons: "*The content of a document must not be considered to be a reservoir from which features pertaining to separate embodiments could be combined in order to artificially create a particular embodiment*" and stated that it had applied the correct standard for Article 123(2) EPC since the subject-matter claimed in the amended claims did not concern an artificially created combination of

features but derived directly and unambiguously from the application as filed. The respondent also cited decision T 1041/07 of 1 October 2009, points 3.4 and 3.5 of the reasons and decision T 1389/08 of 30 July 2010, point 4.2 of the reasons, stating that the skilled person would seriously contemplate combining the most preferred features.

The respondent stated that its arguments in favour of claim 1 of the main request applied *mutatis mutandis* to claim 2 of the main request.

The respondent maintained its arguments in relation to claim 2 of auxiliary request I, which is identical to claim 2 of the main request. It also maintained the arguments it submitted for claim 1 of the main request in relation to claim 1 of auxiliary request I in which the only difference served to overcome some of the appellant's objections.

(i) *Admissibility of auxiliary requests III and IV filed at the oral proceedings on 4 October 2012*

The respondent submitted that auxiliary requests III and IV should be admitted into the proceedings since both requests represented a *bona fide* response to the previous discussions under Article 123(2) EPC. The amendments were simple and easy to handle (deletion of claims, deletion of objected features).

(j) *Auxiliary request IV (Articles 123(2) and 56 EPC)*

The respondent maintained its previous arguments pursuant to Article 123(2) EPC submitted for claim 2 of

the main request. The deletion of the feature at the end of the claim had overcome the remaining objections.

As regards the issue of inventive step the respondent submitted the following.
The respondent cited document D32 and submitted that after a tablet is taken orally it goes from the oesophagus to the stomach, where it disintegrated into small primary particles. The drug dissolved from these particles, with rapid dissolution then being dependent on the size and surface of the particles (D32, page 8). The volume in the stomach was about 50 ml to about 200 ml, depending *inter alia* whether the intake of the tablet took place with a glass of water, and the pH was within the range 1 to 3.5, depending on the circumstances. The respondent cited document D32, page 145, left-hand column. It also submitted that it was of importance how much time a particle spent in the stomach and whether or not the intake of the tablet took place in a fasting state. The pylorus controlled the emptying by occasionally opening, allowing small amounts to leave. The average emptying time of a solid dosage form which disintegrated into small subunits was ninety minutes (document D32, page 146, right-hand column, second paragraph). Only after leaving the stomach would the drug be free from acid-catalysed rearrangement and only after entering the small intestine would it be absorbed. The small intestine was the area where most of the drugs taken orally were absorbed. The extent of absorption in the stomach was not relevant (D32, page 144, right-hand column, page 145 left-hand column, first paragraph). The respondent submitted that the overall teaching of document D32 was that it was not a good idea if the

drug spent too much time in the stomach because this would negatively affect bioavailability.

The respondent also cited document D14, and stated that an acid treatment of DRSP with 0.1 N hydrochloric acid at room temperature converted within 3 hours into a mixture 8:2 isomerised DRSP *versus* active DRSP. Thus, the respondent alleged that increasing the temperature to 37°C would result in an increased rate of isomerisation (i.e. 80% of DRSP would be isomerised within 1 to 1.5 hours).
The respondent also referred to the experimental data D20a, stating that after 60 minutes at pH 1 only 30% of the active DRSP was left, and after 90 minutes at pH 1 only 20%. These data showed similar magnitude of time as those given in document D14.

The respondent also argued that even if taking the comparison with spirorenone as a valid comparison, document D35 disclosed the solubility of spirorenone as less than 5 µm/ml (page 235, right-hand column). This would mean that half of the amount of the total dose of the drug, i.e. 1 mg, would dissolve in the volume of the stomach. The respondent further submitted that if the drug was micronised it would dissolve more rapidly in the stomach and would thus isomerise. Therefore, the skilled person would have serious concerns about making the drug dissolve immediately in gastric juice since this would result in losing half of the dose. Moreover, the respondent argued that if half of the 2 mg DRSP were dissolved, isomerised and absorbed, the inactive isomer would not be detectable according to the method in document D33 since its plasma concentration would be below the required 5ng/ml. The respondent also

submitted that document D32 taught that when a drug was unstable in gastric fluid means should be provided for minimal dissolution in gastric fluid (page 161, right-hand column, second paragraph).

The respondent also submitted that it was immaterial whether document D1 or document D2 was defined as the closest prior art since neither of them disclosed immediate release formulations. Moreover, the fact that DRSP was micronised resulted in a rapid dissolution form. The problem to be solved was to improve bioavailability. The problem to be solved was defined in paragraph [0037] of the patent in suit. The respondent referred to the pharmacokinetic study submitted with its letter of 20 February 2007, in which two tablet formulations had been compared which merely differed in that DRSP was either micronised or non-micronised. A significantly greater amount of active DRSP was absorbed and present in the plasma following oral administration of the tablet with micronised DRSP as compared with the non-micronised DRSP tablet. Neither document D1 nor document D2 addressed the improvement of bioavailability. The respondent also mentioned example 4 of the post-published document D3 in order to further support that it was credible that high bioavailability was achieved with tablets containing 2 mg DRSP.
The respondent submitted that documents D4 to D11 showed micronised steroids as a kind of standard, but that they did not concern acid-sensitive steroids. Thus, they were not relevant. Document D7 related to the effect of micronisation on spironolactone, but spironolactone did not bear a 15β, 16β-methylene group (as was the case with spirorenone and DRSP) and was

stable to the acid juice in the stomach. Document D14 showed that the 15β, 16β-methylene group was responsible for the acid sensitivity of the spirolactone ring in DRSP. Document D14 had investigated the influence of the stereochemistry and the compound bearing a 15α, 16α-methylene was not labile in acid.
Document D28 showed that spironolactone was much less acid-sensitive (page 552, Figure 1, curve pH 2.3) than DRSP. Document D27 showed in scheme 1 that spironolactone did not bear a 15β, 16β-methylene group. Document D27 showed that the γ-lactone of canrenone, similar to that of spironolactone, was stable in acid.
Documents D32 and D23 discouraged the skilled person from micronising acid-sensitive substances. Document D32 explained that acid-sensitive substances should be protected by providing oral forms which do not dissolve too quickly in the stomach (page 161, right-hand column) and document D23 taught that a more rapid dissolution process could result in a decrease in bioavailability for many drugs instable in the acid juice.
Additionally, the respondent denied that DRSP bears a weak acid moiety and argued that the paragraph cited by the appellant (D32, page 144, right-hand column) about absorption in the stomach thus did not apply. The same document D32 also stated that the small intestine was the most important site for absorption in the gastro-intestinal tract (page 138, left-hand column).
Moreover, document D30 taught that progesterone (lipophilic molecules) was absorbed from the intestinal tract (page 950, right-hand column).

The respondent further submitted that the skilled person would not be able to deduce the proposed

solution (concerning micronised DRSP) from the teaching in the Krause documents (D33 to D35). Documents D33 to D35 did not relate to the administration of DRSP but to that of spirorenone. The respondent also stressed that the Krause documents did not concern micronised forms and that they did not teach that spirorenone was truly absorbed in the stomach. In particular, the experiments with monkeys (the pH conditions in the monkeys' stomachs were not necessarily identical to those in humans as shown in the post-published documents D42 and D4) disclosed in document D34 used a microcrystalline suspension a not micronised spirorenone. Additionally, the respondent argued that Figure 5 in document D33 (page 43) did not show curves obtained from a rapid dissolution form. Spirorenone absorbed relatively rapidly after absorption had started from the small intestine. It pointed to the Tmax of 3 hours and to the curve which showed that in about half an hour the plasma concentration had doubled, but this happened only after absorption had actually started (D33, page 43, Table II).

Document D41 showed that the lag time was longer in fed subjects than in fasted subjects, but that the absorption half-life was about the same. This showed that the appreciation of the absorption half-life in Table II of D33 made by the appellant was not correct. The respondent also referred to the curves depicted in document D26 for comparison purposes. Moreover, the respondent stressed that DRSP was studied in the Krause documents as a metabolite *in vivo* of spirorenone. D33 investigated whether a pharmaceutical formulation resistant to gastric juice was necessary to be developed for spirorenone (page 37). Thus, the only

teaching in document D33 which would have interested the skilled person in relation to DRSP was the teaching to be extracted from the *in vitro* experiments showing the acid-catalysed rearrangement of spirorenone and DRSP (Figure 4), in particular, that DSPR isomerised faster than spirorenone. The respondent alleged that Figure 4 showed the "half-life", meaning that the time according to the curves in Figure 4 where the peak height was 50% of its initial value represented 50% of amount transformed. Thus, according to the respondent, "half-life" was achieved at 90 minutes for DRSP *versus* 150 minutes for spirorenone.

Additionally, the respondent stressed that the claim concerned a dose of 2 mg DRSP. Thus, if following document D33 for an appreciation of the aqueous solubility in analogy to spirorenone, 1 mg of DRSP would be dissolved in the gastric juice. This would cause a rapid degradation of more than 25% of the drug. With a micronised DRSP the skilled person would expect to lose more of the dose in view of the rapid dissolution of the micronised particles.
Dissolving the 40 mg spirorenone in the tablets of document D35 would require 8L volume in view of the water solubility value of 5 µg/ml stated on page 235. Additionally, the pharmacokinetic parameters (t_{max} more than 1.3 hours) in document D35 put into question whether spirorenone was absorbed in the stomach. Whether or not DRSP was actually absorbed in the stomach was not told in the prior art. The teaching in document D35 was not applicable to low dose DRSP tablets.

The respondent also stated that decision T 1329/04 of 28 June 2005 did not set the standards for admission of post-published evidence in the assessment of inventive step. The patent in suit defined in paragraph [0037] the problem of improving bioavailability and its plausible solution. The claimed invention was considered to be a *bona fide* solution to the problem to be solved as mentioned in point 10 of decision T 433/05 of 14 June 2007, and the post-published evidence accepted for the assessment of Article 56 EPC. Thus, documents D26 and D3 showed that the problem had indeed been solved.

The respondent clarified that it had not argued that there was a general prejudice in the prior art against the micronisation of DRSP but that the prior art taught away from micronised DRSP as a solution to the technical problem to be solved. Decisions D31 and D40 referred to commercial contraceptive products and not to all products containing steroids (without specifying acid-sensitivity). There was no information that steroids such as noresthisterone, levonogestrel or gestodene (D4, pages 65, 66) had been micronised. Moreover, as regards documents D33 to D35, it was reflected in decision D31, pages 12 to 14 that during the course of strategic meetings Krause had cautioned his colleagues that the studies were with spirorenone and that there was little information on DRSP. D31 showed that the skilled person would have been concerned to lose DRSP in the stomach and that he would have been surprised when finding that a good bioavailability for DRSP was achieved with immediate release tablets.

Additionally, the respondent stressed that claim 1 of auxiliary request IV should be read in the light of the description as relating to immediate release oral dosage forms. The tablets claimed in claim 1 did not encompass enteric coated tablets. The respondent argued that the appellant's allegation that the tablets claimed in claim 1 were enteric coated was inadmissible. Such an interpretation of the claim was illogical and did not make sense because it was in clear contradiction with the whole content of the description, namely paragraphs [0038], [0040] and [0075] of the patent in suit. The respondent cited the book "Case Law of the Boards of Appeal of the EPO", 6th edition 2010, part II.B.5, "Interpretation of claims" (point 5.1). The respondent stated that analogous reasons applied to tablets containing a matrix embedded with the drugs, and that such tablets were not addressed by the claim. The respondent also argued that the appellant's objections in relation to the interpretation of the claims should be disregarded, since it had raised them for the first time during the oral proceedings and had thus changed its case in relation to its previous submissions during the opposition and appeal proceedings. In particular, the respondent referred to the statement of grounds for opposition dated 27 June 2006, the appellant's letters dated 17 December 2007 and 26 August 2008, and the decision under appeal, page 8. Moreover, there was no dispute before the oral proceedings in relation to the term "micronised". The objection raised by the appellant in relation to this term was in fact an objection under Article 84 EPC. Such an objection was not admissible since the term was already in the granted claims and Article 84 EPC was

not within the grounds for opposition under Article 100 EPC.

Additionally, the respondent submitted that the term "micronised" was known to the skilled person and that its meaning was disclosed in the prior art. Moreover, the skilled person would understand it as leading to rapid dissolution. The respondent cited the particle sizes for micronised drugs in document D7 (abstract, median particle size 2.21 µm), document D6 (page 213, left-hand column, median particle size 3 µm), document D8 (abstract, 1-15 µm and document D9 (page 623, left-hand column, second full paragraph, geometric mean diameter 11 +/- 1.7 µm). The respondent further argued that the skilled person would be able by way of retro-engineering of the claimed tablets to establish the particle size. What mattered was that the claim defined that the tablets contained the micronised drugs. The tablets claimed were immediate-release tablets. Moreover, the tablets should work at the different pH of the gastric juice, as was the case with the claimed tablets. The choice of pH 1 was standard for *in vitro* experiments investigating acid sensitivity to acid juice.

Whereas the respondent had stated during the oral proceedings on 4 December 2012 that either document D1 or document D2 could be defined as the closest prior art, it changed its reasoning during the oral proceedings on 20 March 2013. In particular it stated that the closest prior art could not be represented by any tablet containing DRSP and estradiol. The tablet had to be suitable for hormone replacement therapy (HRT). Therefore, document D2 which addressed the treatment of severe premenstrual dysphoric disorder

(PMDD), was not appropriate as the starting point. Document D1 concerned HRT, but there was no pointer to the specific combination of DRSP and estradiol which appeared in two lists of options in claims 6 and 7, respectively. It further cited paragraphs [0005] and [0006] of the patent in suit and argued that previous to the present invention nobody had proposed micronised progesterone for HRT.

XXVIII. The appellant (opponent) requested that the decision under appeal be set aside and that European patent No. 1257280 be revoked. It further requested that documents D45 to D57, filed with the respondent's letter dated 4 October 2012, not be admitted into the proceedings.

XXIX. The respondent (patent proprietor) requested that the patent be maintained in amended form on the basis of the main request or, alternatively, on the basis of one of the auxiliary requests I and II filed on 4 October 2012, or one of the auxiliary request III and IV submitted during oral proceedings on 4 December 2012. It further requested that:

- the objection of lack of inventive step relying on public prior use in accordance with the findings of decision T 7/07 (D58) not be admitted into the appeal proceedings;
- the objection of the extension of subject-matter not be admitted into the appeal proceedings in so far as it constituted a new ground for opposition under Article 100(c) EPC or a belated objection under Article 123(2) EPC;
- the belated objections under Article 83 EPC not be admitted into the appeal proceedings;

- the submissions under Article 115 EPC filed with letter of 15 November 2012 by a third party and its annexes (documents D64 and D65) not be admitted into the appeal proceedings;
- documents D45 to D57 be admitted into the appeal proceedings;
- documents D59 to D61 filed with the appellant's letter of 4 October 2012 not be admitted into the appeal proceedings;
- the submissions under Article 115 EPC filed with letter of 20 February 2013 by a third party and its annexes (therein referred to as documents D59 to D63) not be admitted into the appeal proceedings.

Reasons for the Decision

1. *Authorisation given to Mr Schön*

With letter dated 2 November 2012, the appellant informed the board and the respondent that Mr Schön, a professional representative, would represent the appellant jointly with Mr Markvardsen, the professional representative already acting on behalf of the appellant. Mr Schön's entitlement to act as a representative for the appellant was contested by the respondent at the beginning of the oral proceedings. The respondent argued that the authorisation dated 2 November 2012 did not indicate the signatory’s name and entitlement to sign contrary to the requirements set out on the reverse side of EPO Form 1003.

As can be inferred from Rule 152(10) EPC, a party may be jointly represented by several representatives. The

question to be decided is whether the communication of Mr Schön's appointment by letter dated 2 November 2012 together with a copy of an authorisation signed by two employees of the appellant entitled Mr Schön to act as joint representative for the appellant in the present appeal proceedings.

Professional representatives who identify themselves as such are required pursuant to Rule 152(1) together with Article 1 of the Decision of the President of the European Patent Office dated 12 July 2007 on the filing of authorisations (OJ EPO 2007, Special edition No. 3, 128; hereinafter "decision") to file a signed authorisation in particular cases only. On the one hand, the filing of a signed authorisation (original and one copy) is required in the event of a change of representative involving professional representatives who are not members of the same association (Article 1(2) of the decision). On the other hand, the European Patent Office may require an authorisation to be produced if the circumstances of a particular case necessitate this, particularly in case of doubt as to the professional representative's entitlement to act (Article 1(3) of the decision).

The appointment of Mr Schön as joint representative is not a change of representative within the meaning of Article 1(2) of the decision. Thus, in order to represent the appellant, Mr Schön was not required to file a signed authorisation on the basis of Article 1(2) of the decision.

The respondent, however, argued that no indication of the signatories' names and of their entitlement to sign

was given in the authorisation dated 2 November 2012 appointing Mr Schön. It was therefore doubtful whether the signatories were entitled to sign the authorisation, either by law or in accordance with the articles of association or equivalent of the appellant. An authorisation bearing the signature of persons not entitled to sign was not valid. In view of documents D66 to D68 submitted by the appellant on 4 December 2012, the board had however no reason to believe that the signatories of the authorisation dated 2 November 2012 were not empowered to appoint Mr Schön as representative for the appellant. Consequently, the board also had no reason to doubt Mr Schön's entitlement to act for the appellant. The circumstances of the particular case thus did not necessitate the production of a (further) authorisation in accordance with Article 1(3) of the Decision of the President of the European Patent Office dated 12 July 2007. The board thus concluded that Mr Schön was duly authorised to represent the appellant in addition to Mr Markvardsen.

The respondent also referred to the communication on matters concerning representation before the EPO (OJ EPO 4/1978, 281) cited on the reverse side of EPO Form 1003. Leaving aside the question of whether this communication is still applicable in view of Article 7(1), second sentence, of the Revision Act of 29 November 2000 and the decisions of the Administrative Council of 28 June 2001 (OJ EPO 2007, Special edition No. 1, 197) and 7 December 2006 (OJ EPO 2007, Special edition No. 1, 89), it certainly does not impose stricter requirements on professional representatives regarding the communication of their

appointment in proceedings before the European Patent Office than the decision referred to above.

2. *Admissibility*

2.1 The appeal is admissible.

2.2 *Admission of the objection of lack of inventive step relying on public prior use in accordance with the findings of decision T 07/07*

2.2.1 Article 13(1) RPBA provides that any amendment to a party's case after it has filed its grounds of appeal or reply may be admitted and considered at the board's discretion which is to be exercised in view of *inter alia* the complexity of the new subject-matter submitted, the current state of the proceedings and the need for procedural economy.

Article 13(3) RPBA provides that amendments sought to be made after oral proceedings have been arranged shall not be admitted if they raise issues which the Board or the other party or parties cannot reasonably be expected to deal with without adjournment of the oral proceedings.

2.2.2 The US decisions D31 of 3 March 2008 and D40 of 5 August 2009 were long known to the appellant.

The board expressed a preliminary opinion in its communication sent on 11 June 2012 as an annex to the summons to oral proceedings. In particular, the board stated that the US court decision D31 and the corresponding US court of appeal decision D40 have no

binding effect on the board in the present appeal case in view of the principles of *res judicata*. The reasons are that the US courts have no jurisdiction in the present case, the proceedings do not relate to the same cause of action, i.e. they do not relate to the same patent (nor to its family document), and the parties involved are not the same (see decision T 167/93, OJ EPO, 1997, 229, in particular points 2.4 and 2.5).

However, the above mentioned communication from the board does not contain any direction within the meaning of Article 12(1)(c) RPBA asking the appellant to raise an objection on lack of inventive step in relation to the prior use of Yasmin^{R}. In fact, such an objection could have been filed and substantiated earlier in the proceedings.
The appellant's objection of lack of inventive step based on the prior use of Yasmin^{R} was filed on 4 October 2012. However, decision T 7/07 of 7 July 2011 was sent to the parties on 10 November 2011 and made accessible to the public via the online file immediately thereafter.

2.2.3 Therefore, there is no valid justification for the late filing of the objection based on the prior use of Yasmin^{R}, which represents a substantial change of the appellant's case and renders the appeal more complex only two months before the oral proceedings scheduled for 4 December 2012.

2.2.4 Consequently, the objection of lack of inventive step relying on public prior use in accordance with the findings of decision T 7/07 is not admitted into the proceedings (Article 13(1) RPBA).

2.3 *Admission of documents D48 to D56*

As a result of the non-admission of the late-filed objection of lack of inventive step relying on public prior use in accordance with the findings of decision T 7/07, documents D48 to D56, which were filed by the respondent as a precautionary measure in response to the appellant's late-filed objection, were not admitted into the proceedings.

2.4 *Admission of documents D45, D46, D47 and D62*

Documents D45 and D57, and the experimental data D46 and D47, were submitted as evidence intended *inter alia* to prevent objections within the meaning of Article 83 EPC concerning the amended claims with a particular dissolution profile. These documents are admitted into the proceedings since they are *prima facie* relevant at least for the issue of sufficiency of disclosure (Article 83 EPC), which the board considered to be within the framework of the present appeal proceedings (see the minutes of the oral proceedings on 4 October 2012).

Moreover, the copies from the Handbook "Lehrbuch des pharmazeutischen Technologie" (D62) reflect the general knowledge of the skilled person. Therefore, D62 is admitted into the proceedings.

The scientific publication D57, which relates to "The Development of USP Dissolution Release Standards", also reflects general knowledge in the technical field of

the patent in suit. Therefore, it is admitted into the proceedings.

2.5 *Admission of documents D59 to D61*

Documents D59 to D60 are copies of opposition division decisions which are not relevant for the present case. Therefore they are not admitted into the proceedings.

Document D61 relates to an international patent application published long after the publication date of the application from which the patent in suit derives. Therefore, D61 is not admitted into the proceedings.

2.6 *Admission of third-party observations under Article 115 EPC*

2.6.1 A third party within the meaning of Article 115 EPC is not a party to the proceedings. Therefore, the admission into the appeal proceedings of third-party observations filed in the course of these proceedings is at the board's discretion. When exercising its discretion the board took into account that it should not accord the third party within the meaning of Article 115 EPC more favourable treatment than would be given to an actual party seeking to introduce such submissions at that stage of the proceedings.

2.6.2 The third-party observations filed with the letter dated 15 November 2012, i.e. less than one month before the oral proceedings which took place on 4 December 2012, as well as the third-party observations filed with letter dated 20 February 2013, i.e. one month

before the continuation of the oral proceedings which took place on 20 March 2013, are not admitted into the proceedings since their admission would have accorded the third party within the meaning of Article 115 EPC more favourable treatment than would have been given to an actual party. There is no justification for such a late filing. These observations contain *inter alia* new submissions which would, if admitted at that late stage of the proceedings, have compromised the fairness of the proceedings.

2.6.3 However, the two pages of the Handbook "*Arzneiformlehre*" (D64) form part of the general knowledge of the skilled person. Moreover, D64 merely confirms the knowledge in documents already on file and thus does not introduce any unexpected change in the case. Therefore, there are no objective reasons to deny the admission of D64.

Consequently, document D64 is admitted into the proceedings.

2.7 *Admission of the main request and auxiliary requests I and II filed with the letter of 4 October 2012, auxiliary requests III and IV filed at the oral proceedings on 4 December 2012, and objections under Article 123(2) EPC*

2.7.1 The opposition division had concluded in its interlocutory decision that the main request filed with the letter of 9 October 2008 met the requirements of Article 123(2) EPC. It is the board's principal task to review the opposition division's decision as to its merits. Additionally, the appellant had raised

objections within the meaning of Article 123(2) EPC with its letter dated 4 October 2013.

Decision T 1421/05, which has been cited by the respondent, is not relevant to the present case since the circumstances of both cases are very different. T 1421/05 dealt with a second appeal in a case which had been previously remitted to the department of first instance after the board had decided on a first appeal in relation to the formal requirements of amended claims.

In relation to the findings of decision T 515/04, cited by the respondent, it has to be said that, although Article 100(c) EPC is not within the framework of the present appeal (it was not invoked as a ground of opposition), the objections under Article 123(2) EPC have to be investigated for the amended claims. The reasons lie in the fact that amendments to claims introduced in the course of opposition proceedings have to be fully examined in relation to Article 123(2) and (3) EPC.

2.7.2 Additionally, the amended claims in the main request and auxiliary requests I to IV were filed for the first time in the appeal proceedings and incorporate features from the description which were not present in the granted claims. Therefore, the amended claims must be reviewed by the board under Articles 123(2) and (3) EPC.

2.7.3 The main request and auxiliary requests I and II filed with the respondent's letter dated 4 October 2012 are admitted into the proceedings since they are *inter alia*

an attempt to pre-empt objections under Article 123(2) EPC to the main request previously on file. Furthermore, the sets of claims filed with the letter dated 4 October 2012 represent a fair attempt to simplify the case by deleting several independent claims.

In view of the above, the main request and auxiliary requests I and II are admitted into the proceedings.

2.7.4 Auxiliary requests III and IV were filed at the oral proceedings on 4 December 2012 after the discussion on the issue of added subject-matter (Article 123(2) EPC) had taken place for the main request and auxiliary requests I and II filed with the letter dated 4 October 2012.

Auxiliary request III contains a single claim only, which differs from claim 1 of the main request in that the expression "or sprayed from a solution onto the surface of inert carrier particles" had been deleted. The objections raised against the feature concerning the dissolution profile in claim 1 of the main request directly apply to claim 1 of auxiliary request III, which is not *prima facie* allowable. Therefore, auxiliary request III is not admitted into the proceedings.

Auxiliary request IV filed at the oral proceedings on December 2012 contains a single claim only, which differs from claim 2 of the main request in that the expression "or sprayed from a solution onto the surface of inert carrier particles" had been deleted. Claim 1 of auxiliary request IV does not *prima facie* raise new

issues. Moreover, the amendment introduced corresponded to a direct reply to the objections under Article 123(2) EPC against claim 2 of the main request.

Therefore, auxiliary request IV is admitted into the proceedings.

3. *Allowability of the main request and auxiliary requests I, II and IV under Article 123 EPC*

3.1 *Main request*

3.1.1 Claim 1 of the main request relates to a tablet comprising 1 mg estradiol and 2 mg drospirenone (DRSP) and a pharmaceutically acceptable excipient or carrier. Moreover, claim 1 further requires that "drospirenone is in a form having rapid dissolution such that at least 70% of said drospirenone is dissolved within 30 minutes when **the tablet** is subjected to dissolution testing in 900 ml of water at 37°C using USP XXIII Paddle Method II operated at a stirring rate of 50 rpm" (emphasis added).

In the description of the application as filed it is stated that: "The term "rapid dissolution" is defined as the dissolution of at least 70% over about 30 minutes … of drospirenone **from a tablet preparation containing 3 mg of drospirenone** in 900 ml of water at 37°C determined…" (page 7) (emphasis added). This particular dissolution profile appertains to a tablet preparation containing a particular amount of DRSP, whereas in claim 1 the profile is attributed to **tablets** containing a different amount of DRSP, namely **2 mg**. Therefore, the amendment relates to an unallowable

intermediate generalisation since it introduces subject-matter going beyond the content of the application as filed (Article 123(2) EPC).

3.1.2 The respondent submitted that the dissolution profile was of general applicability and that tablets containing 2 mg DRSP would necessarily be able to attain the dissolution profile of tablet preparations containing 3 mg DRSP. It also referred to the experimental data D46 and D47.

The respondent's allegation that the dissolution profile reflects a standard dissolution profile of general applicability for the USP XXIII Paddle Method is rebutted by document D57 (page 985, Table I), which mentions a different profile, namely, that ≥ 75% of the drug are dissolved in ≤ 45 minutes".

It is not denied that it is in principle feasible (see document D45) to achieve similar dissolution profiles with different physical forms of DRSP in the dosage form, but the application as filed does not disclose directly and unambiguously that the specific dissolution profile on page 7 applies to any of the tablets containing DRSP (in different amounts) and estradiol.

Therefore, even considering the content of the description in the light of the general knowledge of the person skilled in the art as represented by documents D45 and D57, the technical information contained in the amended claim is not implicitly disclosed in the application as filed in a direct and unambiguous manner.

The experimental data D46 and D47 submitted by the respondent concern two specific tablets: "coated tablet 2 mg + 1 mg medium red" and "coated tablet 3 mg + 1 mg light pink". Documents D46 and D47 do not state the exact constitution of the tablets tested except that they are film-coated tablets and that they contain the stated amounts of the drugs. Moreover, they do not state what kind of DRSP primary particles are to be dissolved (micronised, particles sprayed from a solution onto the surface of an inert carrier), or which is the size of the particles in the tablets. Therefore, the tests results in documents D46 and D47 cannot serve to support the respondent's view, since it cannot be concluded whether the results are of general applicability. Moreover, documents D46 and D47 do not represent the general knowledge of the skilled person.

3.1.3 Consequently, the main request fails since claim 1 does not meet the requirements of Article 123(2) EPC.

3.2 *Auxiliary requests I and II*

3.2.1 Claim 2 of auxiliary request I and claim 1 of auxiliary request II are identical.

3.2.2 Claim 2 of auxiliary request I singles out tablets containing 1 mg estradiol sprayed from a solution onto the surface of an inert carrier and 2 mg micronised DRSP. The application as filed does not specifically disclose such tablets. In order to arrive at this specific combination of features now appearing in claim 2 of auxiliary request I, the skilled person has to combine features concerning the physical form of the

active ingredients which are disclosed only for dosage forms in general (for oral administration of an estrogen, page 8, second full paragraph, of the application as filed), together with the choice of the dosage form as a tablet and the choice of the specific amounts of the two specific drugs. Page 15, second paragraph, of the application as filed discloses in general terms dosage forms containing DRSP and estradiol in micronised form or sprayed from a solution onto particles of an inert carrier, but only in connection with the condition that they are "in admixture with one or more pharmaceutically acceptable excipients **that promote dissolution of the drospirenone**". Therefore, this passage cannot serve as an allowable basis for the tablets appearing in claim 2 of auxiliary request I, which does not include any condition to the choice of excipients present in the claimed tablet apart from that they should be pharmaceutically acceptable.

The claim concerns an artificially created combination of features, since the whole application as filed discloses micronised estradiol as preferred embodiment, and estradiol sprayed from a solution onto the surface of inert particles is not singularised, except in connection with the specification of the other excipients present in the dosage form.

3.2.3 Therefore, claim 2 of auxiliary request I does not meet the requirements of Article 123(2) EPC. This conclusion directly applies to claim 1 of auxiliary request I which has an identical wording.

3.3 *Auxiliary request IV*

3.3.1 Auxiliary request IV contains a single claim. Claim 1 derives from granted claim 3, which is an independent claim directed to a pharmaceutical composition in the form of an oral dosage form comprising as active drugs an estrogen, other than ethinyl estradiol, and micronised DRSP.

3.3.2 The specification in the amended claim of the estrogen as estradiol which is in micronised form finds an allowable basis in the application as filed, since micronised estradiol is disclosed as the preferred estrogen (*inter alia* page 7, line 3 and page 12, line 6). Moreover, there is an individualised disclosure for the specific combination of doses of DRSP and estradiol on page 12, lines 28 and 29 of the application as filed.
Tablets are mentioned as an option for oral dosage forms on page 16, second paragraph of the application as filed, and the examples singularise the combination micronised DRSP and micronised estradiol as the most preferred in tablets, which also singularise the combination of doses specified in the claim (see pages 22, 23, 24, 26 of the application as filed). Therefore, the subject-matter claimed in claim 1 of auxiliary request IV is disclosed directly and unambiguously in the application as filed.

The claim does not represent an arbitrary combination of features from the content of the application as filed, since all the features specified are disclosed as most preferred and the specific combination claimed has been singularised in the application as filed. That

the examples investigating bioavailability used an oral solution for comparative purposes does not change the fact that tablets are the first choice for the oral dosage form disclosed in the application as filed.

3.3.3 Consequently, claim 1 of auxiliary request IV meets the requirements of Article 123(2) EPC. Additionally, since the subject-matter claimed has been restricted in comparison with the subject-matter claimed in claim 3 as granted, the requirements of Article 123(3) EPC have also been met.

4. *Auxiliary request IV (inventive step)*

4.1 Document D2, which discloses the use of DRSP and estradiol for the preparation of medicaments for oral administration of 0.5 mg to less than 5 mg per day DRSP, preferably 1.0 to 4.0 mg, and 1.0 to 3.0 mg per day estradiol, represents the closest prior art (D2, claims 2, 8, 11 and 13, page 4, lines 5, 6, 9, 10, 15). Document D2 discloses that the oral administration is the most preferred form and tablets are the most common dosage form for oral administration. In fact, tablets are disclosed in document D2 as the first of several options (page 5, line 4). Document D2 further discloses that the stated daily dose is preferably administered at once in case of oral administration (page 2, line 10). Therefore D2 discloses tablets containing amounts of the drugs which correspond to the full daily dose in mg stated above.

The specific amounts of 1 mg estradiol and 2 mg DRSP in claim 1 of auxiliary request IV fall within the range of 1 to 3 mg for estradiol and 1 to 4 mg DRSP disclosed

in document D2. Moreover, the patent in suit discloses ranges for the combination estradiol/DRSP, from 1 to 3 mg estradiol and from 0.5 to 4 mg DRSP, without mentioning any particular effect linked to the choice of one particular combination of individualised amounts over the others (paragraph [0063] of the patent in suit). Therefore, the choice of specific amounts of the drugs within the known ranges disclosed in document D2 is arbitrary and can only be considered as an added feature contributing to the novelty of the claimed tablets.

4.2 In the light of the closest prior art the problem to be solved lies in the provision of alternative tablets containing the drugs DRSP and estradiol.

The solution as defined in claim 1 of auxiliary request IV relates to the micronisation of the drugs contained in the tablets.

The problem has been plausibly solved in the light of the description and examples in the patent in suit.

4.3 It has not been disputed that the skilled person knew at the effective date of filing of the patent in suit that estradiol is poorly absorbed (see *inter alia* D4, page 62) and that DRSP is a poorly or sparingly aqueous soluble drug.

4.3.1 Document D4, which is a review article on the bioavailability of orally administered sex steroids used in oral contraception and HRT, teaches the micronisation of estradiol for addressing the problem

of its poor absorption when orally administered (page 62, left-hand column).

4.3.2 The claimed tablets are not delimited by any particular dissolution profile, nor is their constitution defined in the claim apart from the statement concerning the presence of at least a pharmaceutically acceptable excipient or carrier and two micronised drugs. Thus, the actual physical constitution/form of the tablets claimed is not defined. Additionally, the absence of definitions concerning the nature and proportions (in relation to the active ingredients for which particular amounts are specified) of the pharmaceutical excipients or carriers present does not allow to conclude that the tablets claimed must necessarily be tablets promoting immediate release in the stomach so that a high percentage (e.g. 75%) of the amount of each of the two drugs is dissolved in less than 45 minutes in the stomach (see document D45, which has been cited by the respondent for the standard definition of immediate release).

The handbook entitled "Pharmaceutics: The Science of Dosage Design" (D32), which has been repeatedly cited by both parties, reflects the general knowledge of the skilled person. D32 mentions tablets as the first option for the most popular oral dosage forms (last sentence on page 4). Moreover, D32 explains how tablets may contain "formulation additives" (excipients) "which are included for specific functions, such as disintegrants which promote tablet break-up into granules and powder particles in the gastrointestinal tract facilitating drug dissolution and absorption" (page 5, left-hand column, first paragraph). However,

claim 1 of auxiliary request IV is silent regarding the choice and nature of the "formulation additives" to be present.

Additionally, when designing a dosage form, the pharmaceutical technologist has to simultaneously consider several factors and their interdependency (document D32, table 1.3, page 7, page 8, left-hand column, last paragraph). Keeping this in mind, document D32 teaches that "the most suitable drug form and additives can be selected for the formulation of chosen dosage forms" (D32, page 6, last paragraph) and that "the fine milling of poorly soluble drug substances can modify their wetting and dissolution characteristics, important properties during granulation and product performance" (page 7, left-hand column). Document D32 further teaches that "it is now generally accepted that poorly soluble drugs showing a dissolution rate-limiting step in the absorption process will be more readily bioavailable when administered in a finely subdivided form with larger surface than a coarse material" (page 8, left-hand column). Micronised drug particles are in finely subdivided form. D32 teaches micronisation as the technique to be employed (page 8, right-hand column, under the heading solubility) for drugs with limited aqueous solubility, since the other options mentioned in D32 - salt or ester formation - are not directly applicable to DRSP owing to its chemical structure. Document D32 further teaches that "for a drug to be absorbed it must first dissolved in the fluid at the site of absorption. For example, an orally administered drug in tablet form **is not absorbed until drug particles are dissolved or solubilised by the fluids** at some point along the gastrointestinal

tract, depending on the pH-solubility profile of the drug substance", paragraph bridging pages 8 and 9, (emphasis added).

D32 also states on page 9 that "If, however, drug dissolution is slow due to its physicochemical properties or formulation factors, then dissolution may be the rate-limiting step in absorption and influence bioavailability".

4.3.3 Therefore, the skilled person looking for a solution to the problem defined above would have provided the drugs in micronised form by making use of his knowledge in the technical field reflected in documents D32 and D4.

4.3.4 The skilled person knew at the time of filing of the patent in suit from the scientific publication D14 about the acid-catalysed rearrangement of the spirolactone in DRSP. However, the information made available to the skilled person in D14 is that "by treatment with 0.1 N hydrochloric acid at room temperature **within 3 hours**" (emphasis added) the product ratio 8:1 (non-active *versus* active DRSP lactone isomer), which represents the **thermodynamic** equilibrium of the acid-catalysed isomerisation, is attained. However, document D14 does not disclose any information about the actual experimental conditions which concern *inter alia* the solid form of DRSP used, or the relative amounts of DRSP in relation to the 0.1 N hydrochloric acid medium (e.g. as w/v). Moreover, D14 does not include any details concerning **the kinetic of the process of dissolution** of DRSP in the aqueous acidic media. Acid-catalysed isomerisation of the lactone takes place if the drug is dissolved. How much

time needs the drug to dissolve in the acidic media cannot be extracted from document D14. Therefore, the lack of information in document D14 does not allow the conclusion that the skilled person would have been taught away from micronising DRSP.

The actual time of release of the primary drug particles from the tablets is not defined in claim 1 of auxiliary request IV and it depends, *inter alia*, on the form and constitution of the tablet, which is also not defined in the claim. Thus, it would be speculative to assume that the skilled person would extract from the scarcely disclosed details of the experiments in document D14 that micronised DRSP should be avoided as a constituent in tablets able to release DRSP in the stomach. It is not denied, however, that when DRSP primary drug particles are released in the stomach they may encounter a medium with pH 1 (which is a pH comparable to the pH of a 0.1 N HCl aqueous medium), but the time required to release and dissolve the DRSP primary drug particles from conventional tablets cannot be deduced from the experiments in D14. Additionally, the average rate of gastric emptying is 90 minutes, but dosage forms which disintegrate into small subunits (e.g. granules) are emptied from the stomach gradually (D32, page 146, right-hand column). Therefore, the skilled person, who was aware of the existence of an acid-catalysed isomerisation for DRSP according to document D14, would have been careful when preparing the tablets containing DRSP to choose an adequate form as well as adequate excipients, but he would not have been prevented from providing DRSP in micronised form. On the contrary, he would have prioritized micronisation to address the major problem of the poor

aqueous solubility of DRSP, since "a solid dosage form containing a poorly soluble drug must first dissolve in gastric fluid prior to being absorbed rapidly from the small intestine" (D32, page 146, right-hand column, last paragraph).

4.4 Therefore, in view of the above analysis the solution to the problem defined in claim 1 of auxiliary request IV is obvious in the light of the prior art.

4.5 As regards the further arguments submitted by the respondent, the following has been considered.

4.5.1 The scientific publication D33 discloses an *in vitro* experiment to study the acid-catalysed rearrangement of the spirolactone group in spirorenone and in DRSP (which is 1,2-dihydro-spirorenone). The experimental design is disclosed at the end of page 39 under the heading "*In vitro rearrangement*" as follows: "Two millilitres of 0.1 N aqueous hydrochloric acid solution were added to 500 µg of spirorenone and its 1,2-dihydro derivative in a sampling vial of the WISP. After short **ultrasonic treatment** 20 µl of the solution were repetitively injected into the HPLC system". The actual duration of the ultrasonic treatment, which is qualified by the subjective and relative expression "short", remains unclear. "Short" may simply mean until dissolution took place. Therefore, time 0 expressed in minutes in Figures 3 and 4 does not necessarily correspond to time 0 from the first contact of the drug particles with the acidic aqueous medium, but starts with the HPLC measurements after dissolution in the sampling vial and injection in the chromatographic apparatus. Moreover, dissolution only follows after an

ultrasonic treatment has taken place. Accordingly, although the rearrangement of DRSP is shown in document D33 to be faster in relative terms in comparison to the rearrangement of spirorenone (Figures 3 and 4), the time requirements in absolute terms for DRSP particles in order **to dissolve** when put in contact with an acidic medium, and subsequently rearrange, is not disclosed in document D33. Moreover, document D33 does not disclose the physical form of the two drugs employed in the rearrangement experiments (e.g. microcrystalline form, amorphous aggregate, etc.). Additionally, the tablets administered to two healthy male volunteers in document D33 (page 38) contained spirorenone, but D33 does not disclose any experiment with tablets containing DRSP. Therefore, in the light of document D33, the skilled person is neither incited to use nor taught away from using micronised DRSP in tablets for oral administration.

Documents D34 and D35 are less relevant for the skilled person looking for a solution to the problem than document D33, since they do not concern studies of DRSP but of spirorenone. In any case, it must be stressed that none of the three scientific articles mentioned prevents the skilled person from micronising either spirorenone or DRSP.

4.5.2 Additionally, there are essential differences between the dissolution behaviour of a chemical substance (a drug substance), which may be investigated using *in vitro* experiments in liquid media, the dissolution release profile of a drug from a solid dosage form, which may be measured from *in vitro* experiments, and the pharmacokinetic plasma profile of an active

ingredient measured from *in vivo* experiments concerning the oral administration of tablets.

Even if the tablet containing the active substances claimed in claim 1 is a conventional uncoated tablet, or is coated with a non-enteric coating, the solid dosage form has to disintegrate first into granules or aggregates, which disaggregate in order to free the primary particles of the drug, which have to undergo dissolution (D32, page 136, Fig. 9.1). Therefore, the effect attained by micronisation of the drugs on the pharmacokinetic dissolution profile obtained after administration of the tablet *in vivo* is clearly interdependent with other factors deriving from the constitution and form of the solid dosage form which remain undefined in the claim (see document D32, page 8, left-hand column, last paragraph).

4.5.3 The experimental data shown in the Figures 1 to 3 in documents D20a, D20b and D20c submitted by the respondent, which concern *in vitro* dissolution experiments of DRSP from oral formulations containing DRSP micronised and non-micronised, respectively, do not form part of the knowledge of the skilled person at the effective filing date of the patent in suit. They cannot therefore be invoked as support for the argument that the prior art teaches the skilled person away from the solution of including micronised DRSP in tablets. Additionally, there is a lack of information about the experimental conditions concerning *inter alia* the actual oral formulation tested (form, constitution, amounts, actual size of the micronised particles), which does not permit any conclusion directly and

objectively applicable to any of the tablets claimed in claim 1 of auxiliary request IV.

By analogy, observations made by scientists working for the patentee during the development of a particular active substance (as reflected, for instance, in the declarations mentioned in decision D31) do not form part of the knowledge of the skilled person, since said knowledge is not unambiguously derivable from the content of the cited prior art. Thus, the technical knowledge of a particular scientific team which had been acquired during the development of a particular substance, but which has not been published at the time of the effective date of filing of the patent in suit does not reflect the knowledge of the notional skilled person to be taken into account for the assessment of inventive step.

4.5.4 As regards the pharmacokinetic study D26, the respondent has not submitted a full and complete information concerning *inter alia* the form and constitution of the tablets administered in the *in vivo* experiments. Therefore, the conclusions to be extracted from the experimental data in D26 may not be applicable to any of the tablets encompassed by claim 1 of auxiliary request IV. Therefore, the "unexpected" improvement of the bioavailability attained by micronisation of the DRSP cannot be included in the definition of the technical problem to be solved.

4.5.5 Additionally, it is immaterial for the assessment of inventive step according to the problem-solution approach as applied above whether DRSP is actually absorbed, at least partly, in the stomach or only

absorbed in the small intestine, since the cited prior art does not give any certainty to the skilled person in this respect. The skilled person would therefore act according to his knowledge, without making use of his inventive skills. The respondent did not dispute the lack of a general prejudice in the prior art deterring the skilled person from providing tablets containing micronised DRSP.

4.5.6 As regards the dispute about the actual median size of the micronised DRSP contained in the tablets it is immaterial for the assessment of inventive step, since the claim is not delimited by a certain particle size. The description cannot be invoked to delimit a technically meaningful claim. However, although the term "micronised" is a general term, the skilled person would not necessarily consider that coarse fractions of micronised particles are meant since this would not be technically meaningful in the present case.

4.6 Consequently, auxiliary request IV fails for lack of inventive step (Article 56 EPC).

5. Finally, since auxiliary request IV fails for lack of inventive step it is not necessary to decide on the respondent's request for non-admission of the appellant's arguments concerning the issue of Article 83 EPC submitted with the letter dated 19 February 2013.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

N. Maslin U. Oswald