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Datasheet for the decision of 28 February 2023

Case Number: T 2527/19 - 3.3.07

Application Number: 07764936.6

Publication Number: 2040683

IPC: A61K9/20, A61K31/585, A61K31/567, A61K31/525, A61P15/18

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITION CONTAINING A TETRAHYDROFOLIC ACID

Patent Proprietor:
Bayer Intellectual Property GmbH

Opponent:
Laboratorios Léon Farma, S.A.

Headword:
Composition containing a tetrahydrofolic acid / BAYER

Relevant legal provisions:
EPC Art. 123(2), 123(3), 83, 87, 88, 89, 56

Keyword:
Amendments - extension beyond the content of the application as originally filed (no) - broadening of the scope of protection (no)
Sufficiency of disclosure - main request (yes)
Priority - main request (yes)
Inventive step - main request (yes)

Decisions cited:
G 0002/10

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Case Number: T 2527/19 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 28 February 2023

Appellant: (Opponent)	Laboratorios Léon Farma, S.A. Gran Via Carlos III, 98, 7th floor 08028 Barcelona (ES)
Representative:	Neymeyr, Ulrich Theodor Paul Dr. Schön, Neymeyr & Partner mbB Bavariaring 26 80336 München (DE)
Respondent: (Patent Proprietor)	Bayer Intellectual Property GmbH Alfred-Nobel-Strasse 10 40789 Monheim (DE)
Representative:	BIP Patents c/o Bayer Intellectual Property GmbH Alfred-Nobel-Straße 50 40789 Monheim am Rhein (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 1 July 2019 concerning maintenance of the European Patent No. 2040683 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	Y. Podbielski

Summary of Facts and Submissions

I. European patent EP 2 040 683 (hereinafter "the patent") was granted on the basis of 15 claims. The independent claim of the patent as granted read as follows:

"1. A process for the manufacture of a solid oral dosage form comprising
a progestogen, an estrogen, a 5-methyl-(6S)-tetrahydrofolic acid or a pharmaceutically acceptable salt thereof, and at least one pharmaceutical acceptable excipient or carrier, wherein
the *in vitro* dissolution of the progestogen is such that at least 70% is dissolved from the solid oral dosage form within 30 minutes, as determined by the USP XXIX Paddle Method II using water at 37°C as the dissolution media and 50 rpm as the stirring rate, and the solid oral dosage form does not contain vitamin B12,
wherein the process comprises the steps of:

(i) subjecting a progestogen, an estrogen and at least one pharmaceutical acceptable excipient to a granulation process,
(ii) mixing a 5-methyl-(6S)-tetrahydrofolic acid or a pharmaceutically acceptable salt thereof with the granules formed in step (i) at the end of, or near the end of, the granulation process, and
(iii) optionally continuing the granulation process, and
(iv) formulating the granules into solid oral dosage forms."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked inventive step,

it was not sufficiently disclosed and it extended beyond the content of the application as originally filed.

III. The opposition division took the decision that, on the basis of the main request filed as auxiliary request 1 with letter dated 29 June 2018, the patent and the invention to which it related met the requirements of the EPC. The main request corresponded to the patent as granted excepted for description page 13 which was amended by deleting the terms "and, therefore, can be regarded as an "inner phase"" at the end of paragraph [0044].

IV. The decision of the opposition division, posted on 1 July 2019, cited *inter alia* the following documents:

D2: "Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to Calcium L-Methylfolate", THE EFSA JOURNAL, vol. 135, 23 November 2004, pages 1-20
D3: EP 1 044 975 A1
D4: WO 2006/120035 A2
D6: WO 01/15701 A1
D7: WO 01/52857 A1
D9: EP 1 632 237 A2
D10: Ritschel WA and Bauer-Brandl A, "Die Tablette, Handbuch der Entwicklung, Herstellung und Qualitätssicherung", "2. vollständig überarbeitete und erweiterte Auflage", 2002, pages 297-299 and 317-318

V. The opposition division decided in particular as follows:

(a) The main request met the requirements of Articles 123(2), 123(3) and 83 EPC.

(b) The priority claimed was valid, so that D4 was not relevant for the assessment of inventive step. D9 represented the closest prior art. The objective technical problem was the provision of a process for the manufacture of a stable solid oral dosage form comprising progestogen and estrogen, which prevents congenital malformation, and allows rapid dissolution of progestogen. The claimed solution was not obvious in light of the prior art.

VI. The opponent (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the appellant's statement setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the main request as maintained during the first instance proceedings as its main request.

VIII. The following items of evidence were filed by the parties during the appeal proceedings:

(a) Documents filed by the appellant with its statement setting out the grounds of appeal:

D10a: Ritschel WA and Bauer-Brandl A, "Die Tablette, Handbuch der Entwicklung, Herstellung und Qualitätssicherung", "2. vollständig überarbeitete und erweiterte Auflage", 2002, pages 297-299 and 317-318, including the page with the publication year
D11: PubChem compound summary "Dienogest"

(b) Documents cited by the respondent with its reply to the statement setting out the grounds of appeal and submitted on 10 October 2022:

D12: Pubchem compound summary "Drospirenone"
D13: European Pharmacopeia, 5th Edition, Volume 1, 15 June 2004, page 7
D14: US 2002/0128229 A1

IX. Oral proceedings were held before the Board on 28 February 2023.

X. The appellant requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

XI. The respondent requested, as its main request, that the appeal be dismissed, and thus that the patent be maintained as held allowable by the opposition division.

XII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) The main request did not fulfill the requirements of Articles 123(2) and 123(3) EPC. The amended features of claim 1 of the main request represented selections within the original application. Their combination was not directly and unambiguously derivable from the original application. Moreover, the amendment to page 13 of the specification resulted in the deletion of the original teaching regarding the position of the acid in the granules, resulting in a broadening of the teaching compared to the original description and the granted specification.

(b) The main request did not fulfill the requirements of Article 83 EPC. The patent did not provide any teaching on how to prepare a solid dosage form comprising granules with the claimed acid in the inner phase of the granules as defined in granted paragraph [0044]. Furthermore, the patent did not provide sufficient information to ensure the achievement of the contraceptive effect, the avoidance of the toxicity risk due to the acid and the stability of the acid in amorphous form or in the presence of polyvinylpyrrolidone.

(c) The main request was not entitled to priority, so that D4 was relevant for the assessment of inventive step.

(d) The claimed process differed from D9 or D6 as closest prior art in that 5-methyl-(6S)-tetrahydrofolic acid was added and in the timing of its addition in the granulation process. No effect directly linked to the timing of the addition had been substantiated over the whole breadth of the claims. The objective technical problem resided in the provision of an alternative process for producing a contraceptive solid oral dosage form comprising a progestogen, an oestrogen and 5-methyl-(6S)-tetrahydrofolic acid which reduces degradation of 5-methyl-(6S)-tetrahydrofolic acid. The skilled person would have learned from D10 that ingredients sensitive to wet granulation, such as 5-methyl-(6S)-tetrahydrofolic acid, should be added at the end of the granulation process. The solution to the defined problem was therefore obvious starting from D9 or D6 in light of D10.

XIII. The arguments of the respondent, as far as relevant for the present decision, can be summarised as follows:

(a) The subject-matter of claim 1 of the main request was disclosed in original claims 43 and 46 and in preferred embodiments of the original description. The amendment to page 13 of the specification was based on the original application. The main request thus met the requirements of Article 123(2) EPC. The extent of protection was defined by the present clear and unambiguous claims, so that the amendment to the specification did not contravene Article 123(3) EPC.

(b) The claimed process was sufficiently disclosed in the patent.

(c) The main request was entitled to priority, so that D4 was not relevant for the assessment of inventive step.

(d) Starting from D9, the claimed process differed therefrom mainly in that 5-methyl-(6S)-tetrahydrofolic acid was added and in the timing of its addition in the granulation process. The objective technical problem resided in the provision of a process for the manufacture of a formulation containing a progestogen, an estrogen and a tetrahydrofolic acid or a pharmaceutically acceptable salt thereof, that does not mask vitamin B12 deficiency and in which the tetrahydrofolic acid or a pharmaceutically acceptable salt thereof is stable and the progestogen is provided in a fast-release form. None of the cited prior art documents suggested to add the present specific acid to the dosage form, let alone at the end of or

near the end of the granulation process to solve this problem.

Reasons for the Decision

Main request - Patent as granted with exception of amended page 13 (paragraph [0044])

1. Amendments

1.1 Claim 1

1.1.1 Claim 1 of the main request is based on original claims 43 and 46 wherein the following features have been introduced:

(a) the use of 5-methyl-(6S)-tetrahydrofolic acid as specific tetrahydrofolic acid,
(b) the specific in vitro dissolution profile of the progestogen,
(c) the absence of vitamin B12 in the solid oral dosage form, and
(d) the timing of the addition of 5-methyl-(6S)-tetrahydrofolic as being "at the end of, or near the end of, the granulation process".

1.1.2 It was undisputed that these features are disclosed in the original application as follows:

(a) original claim 13 and page 9 lines 26-28,
(b) original claim 18 and the paragraph bridging original pages 5 and 6,
(c) original claim 28 and page 9 lines 33 to 36, and
(d) original page 20 lines 25 and 26.

1.1.3 The appellant however contested that features b) to d) represented preferred embodiments of the invention. According to the appellant these features would require a selection from the original disclosure and their combination would not be originally disclosed. Furthermore the appellant argued that the original application did not directly and unambiguously disclose that a combination of features (a) to (d) would indeed give rise to the technical effect of a contraceptive oral dosage form comprising a progestogen having an *in vitro* immediate release profile and an estrogen, and which provides satisfactory protection from congenital malformations without masking vitamin B12 deficiency. The skilled person would thus be presented with new technical information after the amendment.

1.1.4 Regarding feature b), as stated by the respondent, the choice of water as medium for the *in vitro* dissolution test reflects a preferred embodiment of the invention, since it is the sole medium used in the examples.

In this context the appellant argued that the examples related exclusively to drospirenone. The skilled person, being aware that not all the progestogens mentioned in the patent were soluble in water, would thus not have extrapolated this teaching to any progestogen. Furthermore by restricting the medium to only water (deletion of HCl 0.1N mentioned on page 5 as an alternative medium for the *in vitro* dissolution), the progestogens claimed in claim 1 had been limited to a particular subgroup, namely those soluble in water, which was not originally disclosed. The appellant referred to dienogest which was known to be practically insoluble in water (see D11 point 3.2.2), so that it had been excluded from the subject-matter of claim 1 following the restriction of the medium to only water.

This argument is not convincing. As explained by the respondent, drospirenone itself is known as having a low solubility in water (see D12 point 3.2.4, 1.81 mg/L in water at 25°C which according to the European pharmacopeia is described as "practically insoluble" see D13, table on p7), as have progestogens in general. The skilled person would therefore have considered water as appropriate for any further progestogen as for drospirenone. Furthermore, the appellant has not convincingly demonstrated that a group of progestogen originally encompassed by the claims would no longer be encompassed by amended claim 1 because:

- The claimed parameter does not correspond to the solubility of the progestogen *per se* but to its *in vitro* dissolution rate from the solid oral dosage form within 30 minutes at 37°C. The solubility indications provided in D11 and D12 measured at 25°C may therefore provide some indication as to the ability of the progestogen to achieve this parameter but cannot be considered as a direct evidence thereof, in particular since solubility is usually increasing with increased temperature. The appellant has therefore not convincingly established that dienogest would not achieve the parameter of amended claim 1.

- The appellant has also not provided any evidence that dienogest would fulfill the claimed parameter when measured in HCl 0.1N instead of water, *i.e.* the appellant's assertion that dienogest would have been encompassed by the original claim but not the amended one remains unsubstantiated.

- The appellant's argument is limited to one single example, with no reasoning for further progestogens.

Moreover, the appellant mentioned the restriction in granted claim 1 to a specific dissolution rate of 70%. The Board however observes that granted claim 1 defines the dissolution rate using the same terms as on original page 5 line 34, namely "at least 70%". No restriction has thus been introduced in this respect.

Finally, in relation to the appellant's argument regarding the absence of the definition of the *in vitro* dissolution profile of the estrogen in amended claim 1, the Board observes that, the claimed *in vitro* dissolution profile of the progestogen is disclosed as an individual embodiment in the original description and is not inextricably linked to any specific *in vitro* dissolution profile of the estrogen.

1.1.5 Concerning feature c), the cited passages of the original application (see claim 28 and page 9 lines 33 to 36) do indeed mention the absence of vitamin B12 and/or vitamin B6.

According to the appellant, the feature of the absence of vitamin B12 requires thus a selection from a list. In particular, the skilled person having knowledge of the biochemical pathways involving folates and vitamins B6 and B12 and their impact on the development of anemias, neuropathies and occurrence of neural tube defects, would have appreciated that vitamin B6 and vitamin B12, and thus their absence in the present dosage forms, would be equally important. The skilled person would therefore not have considered the absence of vitamin B12 as being preferred.

As argued by the respondent, the absence of vitamin B6 is however not further discussed in the original application. By contrast, the reasons linked to the absence of vitamin B12, in particular in combination with the addition of 5-methyl-(6S)-tetrahydrofolic acid, are extensively discussed on original page 1 line 34 to page 2 line 6. Hence it is directly and unambiguously derivable from the original application that the absence of vitamin B12 represents the most preferred embodiment for this feature.

When assessing the compliance with the requirements of Article 123(2) EPC, the relevant question is indeed, as underlined by the appellant, whether the amendments remain within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, from the whole of the application as filed (according to the "gold standard" of G 2/10, OJ 2012, 376). In the present case, the appellant refers to the knowledge of very complex biochemical pathways in order to broaden the teaching of the original application. This goes beyond the use of common general knowledge as meant in the context of the gold standard. In the present case, the original application discloses a clear preference for the absence of vitamin B12, for reasons which are in line with the common general knowledge of the skilled person. Whether or not the skilled person may consider the absence of vitamin B6 as equally important from a biochemical point of view cannot override the direct and unambiguous preference indicated in the original application, which is the decisive point in the context of Article 123(2) EPC.

1.1.6 As far as feature d) is concerned, the Board observes that the feature added in present claim 1 indeed

corresponds to a restriction to 2 out of 3 preferred options disclosed in the cited passage of the original application (the option "after" the granulation process was omitted in present claim 1). This mere deletion does, however, not result in the singling out of a particular embodiment.

The appellant considered that this feature would be disclosed on original page 20 in the context of fluidized bed granulation while granted claim 1 related to any granulation process, so that an unallowable intermediate generalisation occurred. The Board disagrees. The passage on original page 20 (see page 20 lines 18-26) is not limited to a fluidised bed granulation process, which is merely a preferred embodiment thereof. The terms "preferably" and "in the case of" have indeed no restrictive meaning for the timing of the addition of 5-methyl-(6S)-tetrahydrofolic acid.

The appellant further argued that the deletion of the feature "after" from the list of the original disclosure introduced a technical contribution which was not originally disclosed, because the respondent relied upon an effect linked to this feature to justify the inventiveness of the claimed process. According to the appellant, as no comparison between an addition "at or near the end of" and "after" the granulation process had been provided, an effect had actually not even been substantiated.

In this regard, the Board observes that in the present case the alleged effect relied upon by the respondent, namely the stability of the tetrahydrofolic acid, is actually described in the passage of the original description in question (see page 20 lines 23-26) for

all the originally disclosed alternatives, *i.e.* for an addition "at the end of, near the end of, or after, the granulation process". The limitation to two out of these three alternatives did thus not provide any technical contribution not originally disclosed.

1.1.7 It follows that the amended features a) to d) correspond to preferred embodiments of the invention. It is furthermore directly and unambiguously derivable from the original application that each of those preferred embodiments apply to any of the otherwise defined solid oral dosage forms and their process of preparation. Their combination in present claim 1 does therefore not result in the subject-matter of claim 1 providing technical information extending beyond the content of the original application.

Regarding the argument of the appellant that the original application would not teach that the present combination of features provides the effect relied upon by the respondent (see above 1.1.3), the Board reiterates that the relevant criteria for assessing the compliance of the amendments with the requirement of Article 123(2) EPC is the "gold standard" (see point 1.1.5 above). For the reasons detailed above, the original application directly and unambiguously discloses the process of granted claim 1, which thus fulfills the requirements of Article 123(2) EPC.

1.2 Paragraph [0044] on page 13 of the description

The appellant objected that the deletion performed in paragraph [0044] of the description would infringe Articles 123(2) and 123(3) EPC.

1.2.1 Article 123(2) EPC

Amended paragraph [0044] corresponds to the original paragraph on page 19 line 24 to page 20 line 3 wherein the embodiments no longer claimed were deleted and the feature "near the end of" was added based on original page 20 lines 25 to 26, and in line with amended claim 1. Furthermore, the explanation that, when added at the end of the granulation process, the acid was an "outer component" was deleted. This deletion is disputed by the appellant.

As argued by the respondent, the deleted passage is however not a feature of the invention recited in the claims as such. The deletion is mere direct consequence of the timing of the tetrahydrofolic acid addition. Therefore it is inherent to the claimed process that, when the acid is added at the end of the granulation process, it becomes an "outer component" of the granules. Hence, the deletion of this passage in the description does not result in the definition of subject-matter extending beyond the original disclosure.

1.2.2 Article 123(3) EPC

The Board observes that the amended paragraph [0044] corresponds to the granted paragraph [0044] wherein the (contradictory) explanation that, when added at the end of the granulation process, the acid was an "inner component" was deleted. As explained above (see 1.2.1), the "position" of the acid is inherent to the timing of its addition. Since the timing of addition is unchanged in the amended paragraph, there is no modification of the scope defined in this passage.

1.3 The remaining granted claims are based on original claims and were not objected to by the appellant. Accordingly, the main request complies with the requirements of Article 123(2) and 123(3) EPC.

2. Sufficiency of disclosure

2.1 Claim 1 relates to a process for the preparation of an oral solid dosage form which comprises a progestogen, an estrogen and 5-methyl-(6S)-tetrahydrofolic acid. Process steps are defined as well as the *in vitro* dissolution profile of the progestogen in the final oral solid dosage form. The present claim does not specify any particular pharmacological effect of the obtained product or any toxicity or stability criterion of any component.

2.2 The Board observes that the patent provides guidance on how to carry out the process of claim 1 and the examples 5 and 6 substantiate that the dissolution profile of the progestogen defined in claim 1 is achieved (see Figure 3 of the patent). Furthermore, the achievement of effects which do not form part of the claims is not a criterion under Article 83 EPC. Finally, the appellant has not provided any evidence substantiating that the process as claimed in claim 1 cannot be carried out.

2.3 The appellant argued in particular that the skilled person would not know how to carry out the claimed process and obtain a solid dosage form from granules wherein the tetrahydrofolic acid would be in the inner phase as described in paragraph [0044] of the granted patent. Such a product, being a final product directly obtained by the claimed process, would be encompassed by claim 1 according to Article 64(2) EPC.

This argument is not convincing, because such a final product is not covered by the present claims. It was undisputed that the "position" of the acid is inherent to the timing of its addition and that when added at the end or near the end of the granulation process, the acid cannot be an inner component of the granules. As the process of claim 1 defines an addition of the acid "at the end, or near the end, of the granulation process", any product directly obtained by the process of claim 1 does not contain the acid as an "inner component" of the granules. Moreover the reference to the acid as being an inner phase component in paragraph [0044] of the patent appears to clearly constitute an erroneous statement in view of the original application (see page 19 lines 33-39 of the original application corresponding to paragraph [0044] of the patent as granted) and is not present in the amended description of the main request.

2.4 Regarding the remaining arguments of the appellant provided during the written proceedings, the Board considers that modifying the amounts of active ingredients forms part of routine practice for the skilled person. Furthermore, the destabilising effect of PVP on 5-methyl-(6S)-tetrahydrofolic acid is identified in the patent, which teaches to maintain in consequence low levels of PVP (see page 8 lines 32 to 36 of the patent). The appellant did not provide any evidence that absolute avoidance of PVP would be essential to maintain the stability of the acid in the claimed oral dosage form.

2.5 As a result, the main request complies with the requirements of Article 83 EPC.

3. Inventive step

3.1 Priority and relevance of document D4 for the assessment of inventive step (Articles 87 to 89 EPC)

The disclosure of the original application cited as support for Article 123(2) EPC is found in an identical manner in the priority document. As the requirements of Article 123(2) EPC are met, the priority claim is valid for the same reasons. Consequently, D4, which was published during the priority year of the present patent, does not form part of the prior art relevant for the assessment of inventive step.

3.2 Closest prior art

3.2.1 The patent relates to a process for the preparation of an oral solid dosage form useful as contraceptive containing a fast-released progestogen and an estrogen. The solid oral dosage form further contains a specific 5-methyl-(6S)-tetrahydrofolic acid to avoid depletion in folates as well as masking vitamin B12 deficiency. The claimed process aims more particularly at stabilizing 5-methyl-(6S)-tetrahydrofolic acid in the final dosage form while maintaining the fast dissolution profile of the progestogen.

3.2.2 During the oral proceedings, the appellant considered D6 or D9 as possible closest prior art documents. In its written submissions, the respondent also developed its arguments starting from D9 as closest prior art.

3.2.3 Document D9 discloses contraceptive oral dosage forms comprising a composition containing a progestogen and an estrogen complexed with cyclodextrin to increase the stability of the estrogen. The composition is prepared

by a standard granulation process (see example 5). However D9 does not provide any information on the release profile of the progestogen. The argument of the appellant that it would necessarily be an immediate release by mere analogy with the examples of the patent is indeed not convincing, since the compositions in both documents are different. D9 does further not mention the addition of any tetrahydrofolic acid.

3.2.4 Document D6 relates to contraceptive oral dosage forms comprising a composition containing drospirenone (*i.e.* a progestogen) and ethinylestradiol (*i.e.* an estrogen) prepared by wet granulation (see example 1) and showing an immediate release of drospirenone (see example 2). As D9, D6 does not mention the addition of any tetrahydrofolic acid.

3.2.5 Both D9 and D6 have the same overall purpose as the present invention, namely the preparation of contraceptive oral dosage forms containing a progestogen and an estrogen. However D6 is additionally concerned with the provision of a fast release of the progestogen. The Board therefore considers that D6 represents the closest prior art document.

3.3 Distinguishing features and related technical effects

3.3.1 The process of claim 1 differs from the one described in example 1 of D6 in that 5-methyl-(6S)-tetrahydrofolic acid is added in the oral dosage form and the addition occurs at the end or near the end of the granulation process.

3.3.2 It was undisputed that 5-methyl-(6S)-tetrahydrofolic acid has generally the effect of protecting from

congenital malformations without masking vitamin B12 deficiency.

3.3.3 The parties however disagreed as to the technical effect resulting from the timing of addition of the acid, in particular its achievement over the whole scope of the claims.

3.3.4 The Board observes that examples 5 and 6 of the patent indicate that, when 5-methyl-(6S)-tetrahydrofolic acid is added at the end or near the end of the wet granulation step, then it has satisfactory stability in the final dosage form upon various storage conditions. Furthermore, paragraph [0048] of the patent states that the dosage forms of the present invention, *i.e.* including those of examples 5 and 6, fulfill the stability criteria defined in the USP XXIX monograph "Folic acid tablets".

3.3.5 The appellant argued that this effect had only been shown in the case of a wet granulation, in particular fluidized bed granulation, while the claims encompassed any granulation process. Furthermore no comparison had been made with an addition during or after granulation. It followed that the effect has not been substantiated, in particular not over the whole scope claimed.

3.3.6 It was common ground that 5-methyl-(6S)-tetrahydrofolic acid is moisture sensitive (see paragraph [0005] of the patent and pages 5 to 6 of D2). In the Board's view, it is therefore credible that an addition earlier in the granulation process would result in decreased stability. Furthermore, it can reasonably be assumed that, if a dry granulation would be carried out, then the destabilising effect due to moisture would not occur. Satisfactory stability would then also be

achieved. Moreover, the appellant has not provided any specific reasons why the effect linked to the timing of the addition of the acid shown in examples 5 and 6 of the patent when using a fluidised bed granulation would not credibly occur for any type of wet granulation. Hence, in the absence of any couter evidence, the Board considers it credible that the effect regarding stability of 5-methyl-(6S)-tetrahydrofolic acid occurs over the whole claimed range. Finally, it is credible that satisfactory stability of 5-methyl-(6S)-tetrahydrofolic acid in the final oral dosage form would result in satisfactory protection from congenital malformations without masking vitamin B12 deficiency when using the final product.

3.4 Objective technical problem

The objective technical problem can thus be formulated as done by the respondent in the reply to the statement of the grounds of appeal (see pages 28 to 29), *i.e.* as the provision of a process for the manufacture of a formulation containing a progestogen, an estrogen and a tetrahydrofolic acid or a pharmaceutically acceptable salt thereof, that does not mask vitamin B12 deficiency and in which the tetrahydrofolic acid or a pharmaceutically acceptable salt thereof is stable and the progestogen is provided in a fast-release form.

3.5 Obviousness of the solution

3.5.1 None of the prior art documents relevant for the assessment of inventive step discloses the preparation of a dosage form containing a progestogen, an estrogen and present tetrahydrofolic acid. The skilled person willing to provide such a dosage form would thus have considered any type of process.

3.5.2 Being aware of the moisture sensitivity of tetrahydrofolic acid, the skilled person would have expected wet granulation to be problematic for the stability of the acid. The skilled person would thus not have been prompted to further develop the wet granulation process disclosed in D6 and also used in D7 or D9. Hence, the skilled person would have considered further commonly used processes, such as dry compression. However as revealed by the comparative examples 1 to 4 of the patent, this would not have solved the above formulated problem as it leads to slow dissolution of the progestogen.

3.5.3 None of the documents cited by the parties (D6, D9, D2, D3, D7 and D10/D10a) teaches to perform a granulation process and add 5-methyl-(6S)-tetrahydrofolic acid at the end of the process, or near the end thereof to obtain a dosage form with satisfactory stability of 5-methyl-(6S)-tetrahydrofolic acid and maintained immediate release of progestogen.

3.5.4 In particular, the Board does not agree with the interpretation of the disclosure on page 317 of D10/D10a made by the appellant. It is indeed specified in the last paragraph of the second column of page 317 that the components are dried mixed, *i.e.* that the ingredient sensitive to wet granulation is added after the granulation process is terminated and does consequently not form part of the granules at all. D10/D10a therefore suggests neither the present timing of the addition of 5-methyl-(6S)-tetrahydrofolic acid nor a dry granulation process.

3.5.5 Hence, the skilled person would not have found in the cited prior art documents any indication of how to solve the problem posed.

3.6 The Board observes that, as the claimed process differs from the one of example 5 of D9 at least by the same distinguishing features as the ones *versus* example 1 of D6, the same reasoning applies *mutatis mutandis* starting from D9 as closest prior art.

3.7 Thus, the main request complies with the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated