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Datasheet for the decision of 12 January 2024

Case Number: T 1324/21 - 3.3.07

Application Number: 17712970.7

Publication Number: 3294270

IPC: A61K9/20, A61K9/28, A61K31/437

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITION CONTAINING RIFAXIMIN ALPHA&DELTA

Patent Proprietor:
Sandoz AG

Opponents:
Alfred E. Tiefenbacher (GmbH & Co. KG)
Alfasigma S.P.A.

Headword:
Rifaximin/SANDOZ

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

Keyword:

Late-filed facts - error in use of discretion at first instance (yes)
Amendment to case - suitability of amendment to address issues
Novelty - availability to the public
Inventive step - suitable starting point in the prior art

Decisions cited:

G 0001/92

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Beschwerdekammern

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Case Number: T 1324/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 12 January 2024

Appellant: (Opponent 1)	Alfred E. Tiefenbacher (GmbH & Co. KG) Van-der-Smissen-Straße 1 22767 Hamburg (DE)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Appellant: (Opponent 2)	Alfasigma S.P.A. 5, Via Ragazzi del '99 40133 Bologna (IT)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Patent Proprietor)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 2 July 2021 concerning maintenance of the European Patent No. 3294270 in amended form.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	A. Jimenez

Summary of Facts and Submissions

I. European patent 3 294 270 ("the patent") was granted on the basis of twelve claims.

The claims as granted related to a pharmaceutical composition comprising rifaximin in polymorphic form α and rifaximin in polymorphic form δ in a molar ratio of 9:1 to 1:9 and a method for preparing a tablet comprising rifaximin form α and rifaximin form δ in a molar ratio from 9:1 to 1:9 involving the compression of a mixture comprising these polymorphic forms of rifaximin.

II. Two oppositions had been filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step and that the claimed invention was not sufficiently disclosed. The opponents filed the appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with the patent proprietor's main request met the requirements of the EPC.

The decision was based on the main request filed on 7 November 2019.

Claim 1 of this main request defined:

"Pharmaceutical composition comprising
(A) rifaximin in polymorphic form α
(D) rifaximin in polymorphic form δ
wherein the molar ratio of (A) rifaximin in polymorphic form α to (D) rifaximin in polymorphic form δ is from 9:1 to 1:9, wherein the pharmaceutical composition comprises

- 45 wt% to 75 wt% of components (A) and (D), and
- 10 wt% to 45 wt% filler."

Claim 9 of the main request defined:

"Method for preparing a tablet comprising
(A) rifaximin in polymorphic form α
(D) rifaximin in polymorphic form δ
wherein the molar ratio of (A) rifaximin in polymorphic form α to (D) rifaximin in polymorphic form δ is from 9:1 to 1:9,
the method comprising the steps of
(i) providing (A) rifaximin in polymorphic form α and (D) rifaximin in polymorphic form δ and optionally one or more further excipients
(ii) optionally dry granulating the mixture from step (i) and optionally one or more further excipients
(iii) compressing the mixture from step (i) or the granulates from step (ii) and optionally further excipients into a tablet,
(iv) optionally coating the tablet."

In its decision the opposition division cited *inter alia* the following documents:

D1: Photographic reproduction of pack and blister of Xifaxan® tablets, batch no. 13012, shelf life: April 2017
D7: Dannalab report dated 18 February 2019
D8: "Fachinformation Xifaxan 550 mg Filmtableten", 2013
D9: Invoice RE201501794, Xifaxan 550 mg Charge 13012
D15: Australian Public Assessment Report for Rifaximin, November 2012
D26: CrystEngComm, 2008, 10, 1074-1081
D28: EP 2 927 235 A1

D36: W.A. Ritschel, A Bauer-Brandl: "Die Tablette", 2nd Ed. Cantor Verlag. 2002, pages 260-261
D44: Declaration by Dr. Giuseppe Claudio Viscomi of 5 May 2021

The opposition division arrived at the following conclusions:

(a) The subject-matter of the main request was new over the prior art, including the public prior use of Xifaxan tablets.

Xifaxan tablets of batch 13012, which according to document D9 were purchased before the priority date, had been shown in document D7 to comprise the polymorph forms α and δ of rifaximin in the ratio and total amount as defined in claim 1 of the main request. However, it had not been demonstrated that these Xifaxan tablets could be analysed to comprise a relevant amount of filler.

The late filed document D44, together with its enclosures, was not admitted for lack of *prima facie* relevance, because the content of document D44 concerned in-house information on the production of Xifaxan tablets which had not been publicly available and which did not demonstrate that the relevant amount of the filler microcrystalline cellulose (MCC) could be determined by analysis of the purchased Xifaxan tablets.

(b) The patent aimed at providing a pharmaceutical composition comprising rifaximin with low systemic bioavailability. Document D28 represented the closest prior art describing compositions for the

same purpose comprising a mixture of rifaximin form α and β instead of a combination of rifaximin form α with form δ as claimed. The prior use of Xifaxan tablets of batch 13012 represented a less relevant starting point in the prior art than document D28, because the presence of rifaximin form δ in the Xifaxan tablets of batch 13012 was contrary to the official documentation relating to Xifaxan approval in documents D8 and D15. The relevant Xifaxan tablets of batch 13012 were thus to be considered defective by their own standard and therefore unsuitable as starting point for the assessment of inventive step.

In view of the experimental results in the patent the problem to be solved in view of document D28 was the provision of an alternative composition comprising rifaximin having a low systemic bioavailability.

As solution to this problem it would not have been obvious for the skilled person to add rifaximin form δ, which was from documents D28 and D26 known to give rise to higher rifaximin absorption.

III. During the appeal proceedings the patent proprietors maintained the main request and upheld auxiliary requests 1-4, which had originally been filed on 7 November 2019 as auxiliary requests 10-13.

Claim 1 of auxiliary request 1 corresponds to claim 9 of the main request.

Claim 1 of auxiliary request 2 additionally defines with respect to claim 1 of auxiliary request 1 that the

the tablet comprises 45 wt% to 75 wt% of components (A) and (D), and 10 wt% to 45 wt% filler.

Claim 1 of auxiliary request 3 additionally defines with respect to claim 1 of auxiliary request 2 that the filler has a water content of 2.5 to 5 wt%.

Claim 1 of auxiliary request 4 additionally defines with respect to claim 1 of auxiliary request 1 that the rifaximin contains water in an amount of 1.5 wt% to 5 wt%, preferably 2 wt% to 4.5 wt%, based on the total amount of rifaximin.

The product claims of the main request are deleted in auxiliary requests 1-4.

IV. The following documents were filed during the appeal proceedings:

A45: submission of 2nd July 2021 in opposition against EP 3 373 914
A46: "Kommentar zur PH EUR.NT 1998", 9th Ed., ZO 5, p. 1-6
A47: Basic & Clinical Pharmacology & Toxicology, 2010; 106: 250–255
A48: Xifaxan 200 Product information, August 2017
A49: The AAPS Journal, Vol. 14, No.4, 2012, p. 915-924
A50: WO 2011/107970
A51: Arthritis Research & Therapy 2012, 14:R115, p. 1-7
A52: Antimicrobial Agents and Chemotherapy, Vol. 60 (3), p. 1830-1833, 2016
A53: International Scholarly Research Network, 2012, Article ID: 195727, p. 1-10

A54: Handbook of Pharmaceutical Excipients, 2006, 5th Ed, p. 132-135

A55: declaration Prof. Dr. K . Ferenz,
A56: FAO monograph "Microcrystalline Cellulose" (2000)
A57: Megazyme® Total Starch Assay Procedure, (2011)

Documents A45-A53 were filed by appellant-opponent 2 with the grounds of appeal.

Documents A54-A57 were filed by appellant-opponent 1 with the grounds of appeal.

V. In its communication pursuant to Article 15(1) RPBA the Board expressed *inter alia* the preliminary opinion that

- documents D44 and A54-A57 were to be admitted into the appeal proceedings, whereas documents A45-A53 were not to be admitted

- the claims of the main request lacked novelty in view of the prior use of Xifaxan tablets of batch 13012 or else lacked an inventive step in view of this prior use as closest prior art.

VI. Oral proceedings were held on 12 January 2024.

VII. The arguments of the opponents relevant to the present decision are summarized as follows:

(a) Admittance of evidence

Document D44 was filed during the first instance proceedings by opponent 2 as evidence regarding the amount and water content of the MCC used for the preparation of Xifaxan tablets. The determination of this amount of MCC in the tablets could not have presented the skilled person with undue burden. The relevance of document D44 was thus evident. The

decision by the opposition division not to admit document D44 for lack of *prima facie* relevance should therefore be overruled.

Document A54 demonstrated that according to the common knowledge MCC was used in tablets as a filler in a concentration of 20-90%. Contrary to the finding in the decision under appeal the Xifaxan tablets of batch 13012 containing MCC as a filler thus must have comprised at least 20% of this compound.

Documents A55-A57 demonstrated that contrary to the finding in the decision under appeal the amount of the filler MCC in the Xifaxan tablets of batch 13012 could be analysed and indeed fell within the range defined in claim 1 of the main request.

Document A45 demonstrated that the patent proprietor had acknowledged in the opposition proceedings against EP 3 373 914 that Xifaxan tablets of batch 13012 comprised the defined rifaximin forms α and δ in the defined amounts.

Document A46 represented evidence of common knowledge in support of the argument that the amount of filler in the Xifaxan tablets of batch 13012 exceeded 10%. Documents A47-A53 supported the argument that the experimental results reported in the patent did not substantiate any effect over the prior art, in particular document D28.

(b) Main request

Xifaxan tablets of batch 13012 had been publicly available as evidenced by documents D1, D2 and D9.

These tablets contained 550 mg rifaximin on a total tablet weight of 1 mg and comprised according to the analysis in document D7 rifaximin of the polymorphic forms α and δ in a molar ratio within the range defined in claim 1 of the main request. Document A54 allowed the conclusion that MCC, which was the only filler and binder comprised in the Xifaxan tablets, must have been present in these tablets in an amount of at least 20% in order to fulfill its function. Moreover, documents D44 and A55-A57 indicated that the Xifaxan tablets of batch 13012 comprised an amount of filler, namely MCC, as defined in claim 1 of the main request and that the skilled person was able to determine this amount of filler in the Xifaxan tablets.

(c) Auxiliary requests

The Xifaxan tablets of batch 13012 comprising rifaximin form α and form δ in the defined ratio represented an available market-product and could as such not be disqualified as a realistic starting point in the prior art. As demonstrated in document D7 and confirmed by the post-published document D18, the statement in document D15 that rifaximin form α, which was used for preparing Xifaxan, does not convert to other forms during manufacture and storage was incorrect. The incorrect statement in document D15 did not justify the conclusion that the Xifaxan tablets of batch 13012 were defective.

The difference of the subject-matter of claim 1 of auxiliary request 1 with the prior use of the Xifaxan tablets of batch 13012 concerned the steps of providing the rifaximin form α and form δ before their compression into a tablet instead of the time

dependent partial conversion of rifaximin form α to form δ in tablets prepared from rifaximin form α. The objective technical problem was the provision of a convenient method of preparing a tablet with the known composition of the Xifaxan tablets of batch 13012. The claimed method was obvious to the skilled person as solution to this problem taking account of the common general knowledge regarding tableting techniques as represented in document D36 or in view of the analogue method for preparing tablets comprising rifaximin forms α and β as described in document D28.

The definition of the amounts of the rifaximin and the filler in the tablet as defined in claim 1 of auxiliary request 2 did not represent a difference with the Xifaxan tablets of batch 13012 and could therefore not contribute to an inventive step.

The water content of the filler or the amount of water contained by the rifaximin as defined in accordance with auxiliary requests 3 and 4 would also not represent any difference with the Xifaxan tablets of batch 13012. These features would furthermore not be associated with any particular effect and could therefore anyway not contribute to an inventive step.

VIII. The arguments of the patent proprietor relevant to the present decision are summarised as follows:

(a) Admittance of evidence

The opposition division had correctly decided that the late filed document D44 lacked *prima facie* relevance, because the content of this document had

not been publicly available and did not demonstrate that the relevant amount of filler in the Xifaxan tablets could be analytically determined. Moreover, document D44 related to Xifaxan tablets of batch 15384 and did therefore not represent evidence regarding the amount of MCC in the tablets of batch 13012.

Documents A54-A57 should have been filed during the proceedings before the opposition division. No justification for the late filing of these documents had been provided. Moreover, document A54 lacked *prima facie* relevance, because the conventional concentration of MCC when used as a filler mentioned in document A54 did not reveal the actual amount of MCC in Xifaxan tablets. Documents A55-A57 also lacked *prima facie* relevance, because the analyses reported in document A55 did not employ conventional methods from the field of pharmacy but relied on techniques from the textile and food industry (A56/A57).

The patent proprietor's arguments presented in a parallel case did not represent evidence of what was actually disclosed by the prior use of Xifaxan as presented in the present case. Document A45 therefore lacked any relevance.

Document A46 was not to be admitted, because it should have been filed during the first instance proceedings and lacked relevance for the same reason as document A54. Documents A47-A53 should have been filed during the first instance proceedings. The argument that the patent did not substantiate any effect over the prior art had already been relied by opponent 2 in the notice of

opposition. No justification for the late filing of documents A47-A53 during the appeal proceedings was evident.

(b) Main request

The amount of the filler (MCC) in the Xifaxan tablets of batch 13012 could not be derived from general knowledge concerning conventional amounts of fillers in tablets as described in document A54. The information on the amount of the MCC used for the Xifaxan tablets of batch 15384 as described in document D44 was not publicly available. Moreover, it could not be concluded that a corresponding amount of the MCC was also contained in the tablets of batch 13012. It had furthermore not been demonstrated that the amount of filler in the Xifaxan tablets could be determined experimentally without undue burden. Documents A55-A57 relied on methods from the textile and food industry, which were not part of the common general knowledge in the field of galenics. The reliance on these methods from different technical fields in documents A55-A57 contradicted the suggestion in the statement of grounds of appeal by opponent 2, that the amount of MCC in the Xifaxan tablets could be determined using ordinary analytical techniques such as a combination of Ion Exchange-HPLC and Size Exclusion HPLC.

(c) Auxiliary requests

The Xifaxan tablets of batch 13012 comprised in addition to rifaximin form α also rifaximin form δ. The presence of rifaximin form δ was contrary to the official documentation on the Xifaxan tablets,

in particular document D15, according to which only rifaximin form α was used for the preparation of the tablets, which would not convert to other forms during manufacture or storage. Document D15 actually recommended to ensure that the commercial preparation of rifaximin is the poorly absorbed polymorphic form α in view of the greater oral bioavailability of other polymorphic forms. The Xifaxan tablets of batch 13012 were therefore defective and unsuitable as starting point for the assessment of inventive step.

Even if the skilled person would consider starting from the Xifaxan tablets of batch 13012 the provision of rifaximin form α and form δ before the compression in to tablets was advantageous over a process which requires a time dependent partial transformation of form α to form δ in the tablets originally prepared form exclusively form α as described for Xifaxan tablets in document D15. The claimed process was not obvious as solution to the problem of providing an improved process, because the prior art provided no motivation no modify the process of document D15.

The same arguments applied with respect to auxiliary requests 2-4. Paragraphs [0090] to [0093] and Figures 3-4 of the patent indicated with respect to the water content of the filler or the rifaximin in the tablet as defined in auxiliary requests 3-4 that rifaximin tablets with a molar ratio of form α to form δ higher than 10:1 and a water content of only 1.2 wt% disintegrate in a different manner from the tablets prepared in accordance with claims. This difference would lead to an undesirable high absorption of the rifaximin

with the higher form α to δ ratio and lower water content.

IX. The opponents (appellants) requested that the decision under appeal be set aside and that the patent be revoked in its entirety.

Opponent 2 further requested that the discretionary decision by the opposition division not to admit document D44 be overruled.

X. The patent proprietor (respondent) requested that the appeals be dismissed (main request).

Subsidiarily, the patent proprietor requested that the patent be maintained on the basis of auxiliary requests 1-4, originally filed as auxiliary requests 10-13 on 7 November 2019 and resubmitted with the reply to the appeals.

The patent proprietor further requested that documents A45-A57 not be admitted into the appeal proceedings.

Reasons for the Decision

1. Admittance of evidence

1.1 Document D44

Document D44 is a declaration by Mr Viscomi, who was from 2002 to 2020 Director of Research and Development of Alfa Wassermann SPA, later Alfasigma SPA, concerning the amount of filler and the nature of the filler present in Xifaxan 550 mg tablets as available on the market before the priority date of the patent (see D44, page 1, lines 1-6). The declaration reports on the

production of Xifaxan 550 mg tablets of batch 15384 with the expiration date of 2018 by Alfasigma in December 2015 (see D44, page 1, Table 1). The declaration cites the used amounts of ingredients from the record of the software managing the manufacturing process of the tablets to calculate an amount of 29.9 wt% for the MCC in the Xifaxan 550 mg tablets (see D44, Table 2 and page 4, lines 4-9 and Table 3). The declaration further refers to a Certificate of Analysis indicating that the used MCC had a water content of 3.2% (see D44, pages 2-3, bridging paragraph).

The opposition division decided not to admit the late filed document D44 for lack of *prima facie* relevance, because the content of document D44 concerned in-house information which had not been publicly available and did not demonstrate that the relevant amount of filler in the Xifaxan tablets could be analytically determined.

The Board notes, however, that it was not in dispute that the Xifaxan tablets of batch 13012 had been publicly available. In view of the public availability of these tablets the finding in the decision under appeal on the *prima facie* lack of relevance of the in-house information in document D44 regarding the amount of filler used for preparing the tablet would in the Board's view only seem reasonable, if it were justified to assume that the actual analysis of the amount of filler in the tablets would present the skilled person with undue burden. However, the Board finds no basis for this assumption.

The patent proprietor argued during the appeal proceedings that document D44 refers to the record of production of Xifaxan tablets of batch 15384 and

therefore lacked relevance regarding the prior use of the tablets of batch 13012. However, the declaration in document D44 specifically addresses the amount of the filler and nature of the filler present in Xifaxan 550 mg tablets as available on the market before the priority date of the patent. In this context the Board finds no ground for doubt that the record for the production of batch 15384 cited in document D44 was representative for the Xifaxan 550 mg tablets available on the market, including the tablets of batch 13012.

Accordingly, the Board has admitted document D44 into the appeal proceedings under Article 12(6) RPBA.

1.2 Documents A54-A57

Documents A54-A57 were filed by appellant-opponent 1 with the statement of grounds of appeal. They constitute an amendment to appellant-opponent 1's under Article 12(4) RPBA which may be admitted at the discretion of the Board.

Document A54 represents hand-book information that MCC is used as a filler in capsules and tablets in a concentration of 20-90% (see page 132, Table 1).

Documents A55-A57 represent evidence that the Xifaxan tablets of batch 13012 could be analysed to comprise a MCC content of 28.2-29.0% on the basis of dry MCC or 29.4-30.1% on the basis of MCC with max. 7% water (see A55, page 9, "Results/Summary table") using methods which were available at the relevant time (see A56 and A57).

The Board considers the filing of documents A54-A57 justified as reaction to the finding in the decision

under appeal that a mere expectation of an amount of filler (MCC) of more than 10% in Xifaxan tablets did not qualify as a direct and unambiguous disclosure of the amount of filler in these tablets and the opposition division's rejection of the admittance of document D44.

The Board considers document A54 *prima facie* relevant to the appeal proceedings, because document A54 presents evidence of the common knowledge regarding the amount of MCC used as binder or filler in tablets, whereas in the appeal proceedings the amount of MCC as the filler in Xifaxan tablets of batch 13012 is in dispute.

The Board also considers documents A55-A57 *prima facie* relevant, because these documents demonstrate that the amount of MCC as the filler in Xifaxan tablets of batch 13012 can be experimentally determined. The patent proprietor argued that these documents lacked relevance, because they refer to analytical methods used in the textile or food industry and thus did not form part of the common general knowledge that the skilled person in the field of galenics could in line with the considerations in G 1/92 (reasons 1.4) apply for determining the amount of MCC in the Xifaxan tablets of batch 13012. The Board finds this objection not convincing, because the the skilled person in the field of galenic could nevertheless retrieve the analytical methods of documents A56 and A57 used in document A55, whereas their application for determining the amount of MCC in the Xifaxan tablets has not been demonstrated to involve undue burden.

Accordingly, the Board has admitted documents A54-A57 into the appeal proceedings under Article 12(4) RPBA.

1.3 Documents A45-A53

Documents A45-A53 were filed by appellant-opponent 2 with the grounds of appeal.

In its communication pursuant to Article 15(1) RPBA the Board explained its preliminary opinion that documents A45-A53 were not to be admitted into the appeal proceedings, because these documents lacked relevance and because their late filing was not justified. No new arguments were submitted in response to the Board's preliminary opinion.

The Board has therefore confirmed its preliminary opinion not to admit documents A45-A53 into the appeal proceedings under Article 12(4).

2. Main request - Novelty

2.1 The finding in the decision under appeal that the Xifaxan tablets of batch 13012 represent prior art under Article 54(2) EPC and have been demonstrated to comprise the polymorph forms α and δ of rifaximin in the ratio and amount as defined in claim 1 of the main request, has not been contested during the appeal proceedings. The dispute regarding the requirement of novelty of the subject-matter of claim 1 of the main request with respect to the relevant Xifaxan tablets of batch 13012 thus exclusively concerned the question whether these tablets also anticipated the remaining feature of an amount of filler in the range of 10 wt% to 45 wt%.

2.2 The declaration in document D44 reports that Xifaxan 550 mg tablets as available on the market before the

priority date of the patent had been prepared using the filler MCC with a water content of 3.2% in an amount which corresponded to 29.9 wt% of filler in the tablets (see D44: page 1, lines 1-6; pages 2-3, bridging paragraph; page 4, Table 3). Document D44 therefore indicates that the Xifaxan tablets of batch 13012 did indeed comprise an amount of filler as defined in claim 1 of the main request

As explained in section 1.1 above, the declaration in document D44 specifically addresses the amount and nature of the filler present in Xifaxan 550 mg tablets as available on the market before the priority date of the patent. The Board finds no grounds to doubt, that the record for the production of batch 15384 cited in document D44 was in accordance with this declaration representative for the Xifaxan 550 mg tablets available on the market, including the tablets of batch 13012. The patent proprietor's objection that that the declaration in document D44 relies on the record of production for Xifaxan tablets of batch 15384 and therefore lacked relevance regarding the prior use of the tablets of batch 13012 is not therefore not considered convincing.

2.3 According to G 1/92 the composition and internal structure of a product is state of the art, when the product as such is available to the public and can be analysed and reproduced by the skilled person without undue burden (see G 1/92, reasons 1.4 and 2).

The experimental report in document A55 demonstrates that the amount of filler in Xifaxan tablets of batch 13012 could be analysed using methods as described in documents A56 and A57, which were available at the relevant time. Document A55 confirms that using these

methods the Xifaxan tablets of batch 13012 were found to comprise a MCC content of 28.2-29.0% on the basis of dry MCC or 29.4-30.1% on the basis of MCC with max. 7% water (see A55, page 9, "Results/Summary table").

The patent proprietor objected that document A55 does not demonstrate that the amount of MCC in the Xifaxan tablets can be determined by the skilled person in the field of galenics without undue burden, because it applied a method for determining the amount of MCC used according to document A56 in the food industry in combination with a method for removing starch as used according to document A57 in the textile industry.

However, as explained in section 1.2 above, the methods of documents A56 and A57 applied in document A55 were nevertheless retrievable to the skilled person in the field of galenics and their application for determining the amount of MCC in the Xifaxan tablets has not been demonstrated to involve undue burden. In view of the availability of these methods the Board considers that the experimental report in document A55 demonstrates that access to the information regarding the amount of MCC in the Xifaxan tablets of batch 1302 was indeed possible and therefore in line with the considerations in G 1/92 part of the state of the art. The conclusion that the skilled person was able to determine the amount of MCC in the Xifaxan tablets of batch 1302 without undue burden using the methods of document A55 is not affected by the circumstance that the suggestion by opponent 2, that the amount of MCC in the Xifaxan tablets could be determined using a combination of Ion Exchange-HPLC and Size Exclusion HPLC, was subsequently not backed up by evidence.

2.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the main request lacks novelty.

3. Auxiliary request 1 - Inventive step

3.1 Closest prior art

The Xifaxan tablets of batch 13012 represented an approved market product. In this context document D8 reports for Germany 6 February 2013 as date of approval of Xifaxan (see D8, section 9). Document D8 describes Xifaxan to comprise rifaximin in polymorphic form α (see D8, section 5) and attests Xifaxan tablets a shelf-life of 3 years (see D8, section 6.3).

Document D15 represents the Australian public assessment report for rifaximin of November 2012. The document reports substantially higher bioavailability of rifaximin from form δ as compared to form α following administration in dogs (see D15, page 9, Table 3). The document further reports that the currently produced polymorphic form of rifaximin is form α, which would according to the provided evidence not convert to other polymorphic forms during the manufacture or storage of Xifaxan tablets (see D15, pages 9-10, bridging section). Under the heading "Assessment of risks" the document observes the need to ensure that the commercial preparation of rifaximin is the poorly absorbed polymorphic form α in view of the greater oral bioavailability of other polymorphic forms (see D15, page 21).

The Xifaxan tablets of batch 13012 had been purchased according to document D9 on 20 November 2015. In line with the shelf-life reported in document D8 for Xifaxan tablets in general the pack-inscript of the Xifaxan

tablets of batch 13012 shown in document D1 indicates the expiry of these tablets in April 2017.

Document D7 established on the basis of a XRPD pattern as obtained from the Xifaxan tablets of batch 13012 on 17 December 2015 (see D7, page 3, under "Rational") that these tablets comprised the polymorphic forms α and δ of rifaximin in a ratio within the range defined in claim 1 of auxiliary request 1 (see D7, page 8, under "Summary").

Whilst the originally contained rifaximin form α in the Xifaxan tablets of batch 13012 had thus according to document D7 apparently partially converted to form δ by 17 December 2015, these tablets had at that time not yet expired. As a matter of fact, the post-published document D18 (see page 2, lines 12-18) confirms that Xifaxan tablets of a multitude of batches from different countries have turned out to contain significant amounts of rifaximin form δ after storage and that the known tablets did not prevent the conversion of rifaximin form α in form δ during shelf life. Notwithstanding the caution recommended in document D15 regarding rifaximin comprising the more bioavailable form δ, the Xifaxan tablets of batch 13012, which contained on 17 December 2015 rifaximin form α and form δ in the ratio as defined in claim 1, still represented an approved market product.

Contrary to the finding in the decision under appeal the Board considers that this approved market product, which had not expired, cannot be disqualified as a realistic starting point for the assessment of inventive step with respect to the method for preparing tablets comprising corresponding amounts of rifaximin

form α and δ as defined in claim 1 of auxiliary request 1.

3.2 Objective technical problem

The subject-matter of claim 1 of auxiliary request 1 differs from the prior use of the Xifaxan tablets of batch 13012 in the provision of the rifaximin form α and form δ before their compression into a tablet instead of the time dependent partial conversion of rifaximin form α to form δ that results in tablets originally prepared from rifaximin form α.

The claimed method involving the provision of rifaximin form α and form δ before their compression into a tablet evidently allows for the advantage of the instant predetermined provision of the tablets comprising these forms of rifaximin in the defined ratio following their compression into tablets with respect to the time dependent partial conversion of rifaximin form α to form δ in the Xifaxan tablets of batch 13012.

Starting from the Xifaxan tablets of batch 13012 containing rifaximin form α and form δ in the defined ratio the objective technical problem may therefore be seen in the provision of a more convenient and thus improved method for the reproduction of corresponding tablets.

3.3 Assessment of the solution

Faced with the problem of providing a more convenient method for the reproduction of the Xifaxan tablets of batch 13012 containing rifaximin form α and form δ with MCC the skilled person would apply the common general

knowledge in the field of galenics and take account of convenient methods reported in the prior art for preparing related compositions.

The skilled person would be motivated to indeed seek a more convenient method for reproducing these tablets in view of the inconvenience inherently associated with the time dependent conversion of rifaximin form α.

Document D36 represents common general knowledge according to which tablets may be instantly prepared by a dry granulation process involving the dry mixing of the active and auxiliary components, including in particular a binder such as MCC, followed by compressing the ingredients into tablets (see D36, page 261, left column).

Document D28 describes in its example 5 a method for instantly preparing tablets comprising 54 wt% rifaximin of forms α and β in a 85:15 ratio and 33.4 wt% MCC involving the provision of the mixture of these forms α and β which are dry blended with excipients, including the MCC, and subsequently compressed into tablets. Document D28 thus describes the convenient preparation of tablets which in view of their composition are closely related to the Xifaxan tablets of batch 13012 containing rifaximin form α and form δ.

The skilled person would thus arrive at the claimed solution by applying the dry granulation process in accordance with the common general knowledge represented in document D36 to a combination of the *per se* known active components rifaximin form α and form δ or by applying the method described in example 5 of document D28 analogously for preparing the Xifaxan tablets of batch 13012 containing rifaximin form α and

form δ. This solution would therefore seem obvious to the skilled person in view of the prior art.

3.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the auxiliary request lacks an inventive step.

4. Auxiliary requests 2-4 - Inventive step

4.1 Claim 1 of auxiliary request 2 additionally defines with respect to claim 1 of auxiliary request 1 the amounts of the rifaximin and the filler in wt%. As explained in section 2 above these features do no define any additional difference with respect to the closest prior art represented by the Xifaxan tablets of batch 13012 containing rifaximin form α and form δ.

In the absence of any additional distinguishing feature being defined in auxiliary request 2 with respect to the closest prior art the Board concludes that auxiliary request 2 does not meet the requirement of inventive step for the same reason as explained for auxiliary request 1.

4.2 Claim 1 of auxiliary request 3 additionally defines with respect to claim 1 of auxiliary request 2 the water content of the filler.

Claim 1 of auxiliary request 4 additionally defines with respect to claim 1 of auxiliary request 1 the water content of the rifaximin.

In as far as the water content of the filler or the amount of water contained by the rifaximin as defined in accordance with auxiliary requests 3 and 4 represents a difference with the Xifaxan tablets of

batch 13012, no particular effect has been shown to be associated with these features.

The patent mentions in paragraphs [0090] to [0093] a difference in the disintegration of rifaximin tablets prepared in accordance with example 1 of the patent and tablets comprising a molar ratio of form α to form δ higher than 10:1 and a water content of only 1.2 wt%. However, the patent does thereby not indicate any effect that is associated with a difference of the claimed subject-matter with the closest prior art, because the Xifaxan tablets of batch 13012 already contained rifaximin forms α and δ in a molar ratio within the claimed range, which is substantially below the 10:1 as mentioned for the comparative tablets in paragraphs [0090] to [0093] of the patent.

Auxiliary requests 3 and 4 are therefore considered to merely provide arbitrary variations with respect to the methods of auxiliary requests 1 and 2. Following the Board's conclusion that the subject-matter of auxiliary requests 1 and 2 was obvious to the skilled person in view of the prior art, the subject-matter of auxiliary requests 3 and 4 would equally seem obvious to the skilled person. Auxiliary requests 3 and 4 therefore lack an inventive step on the same basis as auxiliary requests 1 and 2.

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:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated