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Datasheet for the decision of 30 January 2024

Case Number: T 0212/22 - 3.3.07

Application Number: 15190823.3

Publication Number: 3017811

IPC: A61K9/20, A61K31/4545, A61P7/02

Language of the proceedings: EN

Title of invention:
APIXABAN FORMULATIONS

Patent Proprietor:
Bristol-Myers Squibb Holdings Ireland Unlimited Company
Pfizer Inc.

Opponents:
Teva Pharmaceutical Industries Ltd.
Sandoz AG
Hamm&Wittkopp Patentanwälte PartmbB
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STADA Arzneimittel AG

Headword:
Apixaban II/BRISTOL-MYERS

Relevant legal provisions:
EPC Art. 54, 56, 112(1)

Keyword:
Novelty - (yes) - implicit disclosure (no)
Inventive step - (no) - comparative example suitable starting point for assessing inventive step
Referral to the Enlarged Board of Appeal - (no)

Decisions cited:
T 1711/16, T 0056/87, T 0414/98, T 0501/04, T 0776/96, T 0297/91, T 0177/98

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Case Number: T 0212/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 30 January 2024

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Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 1 December 2021 revoking European patent No. 3017811 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

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

Summary of Facts and Submissions

I. European patent 3 017 811 ("the patent") was granted on the basis of eleven claims.

Claim 1 as granted defined a tablet comprising up to 5 mg apixaban and a pharmaceutically acceptable diluent or carrier which is obtainable by a process comprising dry granulating a blend of raw materials including crystalline apixaban particles having a D_{90} less than 89 µm as measured by laser light scattering followed by compressing the blend into a tablet and film coating the tablet.

II. Nine oppositions were originally filed against the grant of the patent ("the patent") on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the (earlier) application as filed. Opponent 8 withdrew its opposition during the proceedings before the opposition division.

III. The patent proprietors filed the appeal against the decision of the opposition division to revoke the patent.

The decision of the opposition division was based on the patent as granted (main request) and auxiliary requests 1-7 filed on 2 June 2020.

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

D1: WO 2010/147978 A1
D2: US 2006/0160841 A1
D4: Pharmaceutical Research, 1995, 12(3), 413-420
D7: European Medicines Agency, Committee for Medicinal Products for Human Use, Guidelines on the investigation of bioequivalence, 2010, pages 1/27-27/27
D8: Pharmaceutical Research, 2002, 9(7), 921-925
D9: The AAPS Journal, 2008, 10(2), 306-310
D10: Guidance for Industry, U.S. Department of Health and Human Services, August 2000,1-13
D17: Encyclopedia of Pharmaceutical Technology, Volume 3, Marcel Dekker Inc., 2002, Chapter "Tablet Formulation", 2701-2712
D18: European Journal of Pharmaceutical Sciences, 1999, 9, 117-121
D38: Modern Pharmaceutics, Chapter 10 "Tablet Dosage Forms", Marcel Dekker (G. S. Banker and C. T. Rhodes, Eds., 3rd ed., 1996), 333-359,
D49: Pharmaceutics: The Science of Dosage Form Design, Aulton, 1988, 1-13, 135-173
D58: Molecular Pharmaceutics, 2010, 7(4), 1235-1243
D74: Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Form, FDA, 1997, 1-11 and A-1/A-2
D78: Clinical Pharmcology and Biopharmaceutics Review, 15 February 2012 (Center for drug evaluation and research, application number 202155Orig1s000)
D84: Pharmaceutical Dosage Forms: Tablets, volume 1, 2nd ed., 1989, 1-24
D94: Pharmaceutics: The Science of Dosage Form Design, Aulton, 3rd ed., 2007, 286-291 and 443-449
D104: Journal of Pharmaceutical Sciences, 2004, 93(6), 1375-1381
D112: Declaration of Dr. Jatin Patel, dated 5 May 2017

D115: Expert declaration of Prof. Dr. Henning Blume, dated March 2017
D116: Annual Report 2017 (Form 10-K) of Bristol-Myers Squibb Co.
D117: Husten: "Golden Mean of Anticoagulation", Forbes 28 August 2011
D118: Current Drug Targets, 2012, 13, 863-875
D121: Supplementary expert declaration of Prof. Blume, dated 23 January 2018
D133: Journal of Thrombosis and Haemostasis, 2007, 5, 2368-2375
D135: The AAPS Journal, 2009, 11(4), 740-746
D140: Decision of the District Court of Delaware, USA, dated 5 August 2020
D141: Decision of the Federal Court of Ottawa, Canada, dated 8 January 2021
D142: Affidavit of Prof. Dr. Allan S. Myerson, dated 22 March 2021
D143: Expert declaration of Prof. Dr. Henning Blume, dated 21 March 2021
D145: Expert Report of Professor Frieß, dated 23 August 2021
D149: Eur. J. Pharm. & Biopharm., 2009, 73, 102-106

The opposition division arrived at the following conclusions:

(a) Documents D140 and D141 were not admitted into the proceedings.

(b) The patent as granted complied with the requirements of Articles 123(2), 76(1) and 83 EPC.

The subject-matter of the claims as granted did not enjoy the claimed priority. Document D1 therefore represented prior art under Article 54(2) EPC.

The claimed subject-matter was new over the prior art.

The claimed subject-matter differed from the closest prior art represented by document D1, in particular the tablet of example 7, in view of the defined particle size of the apixaban. The objective technical problem was the provision of an apixaban tablet with improved bioavailability. The claimed subject-matter was obvious as solution to this problem in view of the common general knowledge as to the effect of the particle size on the bioavailability of drugs as well as document D2, which specifically described the preparation of small sized crystalline apixaban in the context of enhancing the bioavailability of sparingly soluble organic compounds.

(c) Auxiliary requests 1-7 did not comply with the requirement of inventive step starting from the tablet of example 7 in document D1 for essentially the same reasons as explained for the main request. The additional difference concerning a dissolution of at least 77% in 30 minutes as defined in accordance with auxiliary request 1 would inherently result from using the small sized crystalline apixaban of document D2 and would correspond to an obvious release profile for solving the objective problem.

IV. With their statement of grounds of appeal the patent proprietors filed a new main request and auxiliary requests 1-3, which correspond to auxiliary requests 1, 3, 5 and 7 on which the decision under appeal was based.

Claim 1 of the main request defines:

"A tablet comprising up to 5 mg apixaban and a pharmaceutically acceptable diluent or carrier, wherein the formulation exhibits dissolution properties such that an amount of the drug equivalent to at least 77% dissolves within 30 minutes, wherein the test result is established as an average of 6 tablets and wherein the dissolution test is performed in an aqueous media buffered to a pH in the range of 1 to 7.4 and controlled at 37° C (±1°C) and wherein the tablet is obtainable by a process comprising the steps of:
(1) blending raw materials comprising crystalline apixaban particles prior to granulation;
(2) granulating the raw materials from the step (1) using a dry granulation process, wherein the crystalline apixaban particles have a D90 less than 89 µm, as measured by laser light scattering;
(3) blending the granules obtained in the step (2) with extragranular raw materials;
(4) compressing the blend from the step (3) into a tablet; and
(5) film coating the tablet from the step (4)."

Auxiliary request 1 differs from the main request in the deletion of dependent claims.

Auxiliary request 2 defines in claim 1 the conditions for the dissolution test more specifically by the features:

"wherein the formulation exhibits dissolution properties such that an amount of the drug equivalent to at least 77% dissolves within 30 minutes, wherein the test result is established as an average of 6

tablets and wherein the dissolution test is performed in 900 ml of dissolution medium containing 0.05 M sodium phosphate at pH 6.8 with 0.05% SDS at 37 °C using USP Apparatus 2 (paddles) at a rotation speed of 75 rpm and the samples are analyzed for apixaban by HPLC at 280 nm."

Auxiliary request 3 additionally defines the tablet by the feature:

"(A tablet) for use in the treatment of a thrombotic disorder (...)".

V. The following further documents were filed during the appeal proceedings:

A152: Expert declaration of Chandra Vema-Varapu, dated 1 December 2021
A153: Lehrbuch der Pharmazeutischen Technologie, Bauer, Kurt H. et al., Stuttgart, Wissenschaftliche Verlagsgesellschaft, 8th ed., 2006, 208-209, 215
A154: Expert declaration of Prof. Martyn Christopher Davies, dated 11 July 2022
A155: Judgment of the UK High Court, [2022] EWHC 1831 (Pat)
A156: Expert Opin. Investig. Drugs, (2008) 17(12), 1937- 1945
A157: Expert Report of Dr Stott, 9 February 2022
A158: Press Release 10 June 2008: "Bristol-Myers Squibb and Pfizer initiate new study in the apixaban Phase 3 clinical trial program"
A159: Decision US Appeal Court of 2021-09-03
A160: Decision CA Federal Court of Appeal of 2022-08-04

Documents A152 and A153 were filed by the patent proprietors with the statement of grounds of appeal.

Document A154 was filed by the patent proprietors with the letter of 22 July 2022.

Documents A155-158 were filed by opponent 1 and partly also by opponents 5 and 6 with their replies to the appeal.

Documents A159-A160 were filed by the patent proprietors with the letter of 5 October 2022.

VI. Opponent 4, KRKA, d.d., Novo mesto withdrew its opposition with the letter of 10 February 2022.

VII. Third party observations (anonymous) were submitted on 19 July 2022.

VIII. In its communication pursuant to Article 15(1) RPBA of 30 June 2023 the Board expressed *inter alia* the preliminary opinion that

- documents D140, D141, A152-155, A157, A159 and A160 were to be admitted, whereas documents A156 and A158 and the third party observations were not to be admitted into the appeal proceedings

- the main request and auxiliary requests 1-3 did not fulfill the requirement of inventive step in view of the closest prior art represented by the immediate release (IR) tablet of comparative example 7 described in document D1.

IX. With the letter of 22 December 2023 the patent proprietors requested that a question be referred to the Enlarged Board of Appeal, if the Board intended to

maintain the preliminary opinion on inventive step in view of the comparative example in document D1.

X. Oral proceedings were held on 30 January 2024.

XI. The arguments of the patent proprietors relevant to the present decision are summarized as follows:

(a) Admittance of documents filed during the appeal proceedings

Documents A152 and A153 were filed in response to the findings in the decision under appeal regarding the interpretation of the experimental results in the patent (A152) and the common general knowledge (A153) and should therefore be admitted.

Document A154 was to be admitted, because it addressed statements in document D145, which had been filed only shortly before the oral hearing held before the opposition division and which was relied upon in the decision under appeal.

Documents A159 and A160 were to be admitted, because these documents related to the appeal decisions confirming the earlier decisions in documents D140 and D141 by US and CA courts on the issue of inventive step of similar subject-matter as defined in the patent in view of similar evidence.

Document A155 related to a first instance UK decision regarding the patent dealing with the issue of inventive step in view of document A156. Documents A156 and A158 referred to clinical studies involving apixaban, but did not provide any

details of apixaban formulations. Document A157 related to a declaration prepared for the UK case and did not represent a response to document A154, which was of a later date. Documents A155-A158 were thus not pertinent to the appeal proceedings and should therefore not be admitted.

The third party observations should not be admitted as they were filed anonymously and lacked relevance.

(b) Main request

The tablet as defined in claim 1 of the main request differed from the IR tablet as described in example 7 of document D1 not only in the defined size distribution of the apixaban particles and the dissolution profile of the drug, but also in the defined crystalline nature of the apixaban particles.

The IR tablet of example 7 of document D1 represented the closest prior art. As confirmed by document A152 the experimental results reported in the patent indicated that tablets with 77% or higher *in vitro* dissolution of the apixaban in 30 minutes showed consistent solution-like bioavailability. The objective technical problem starting from this prior art was therefore the provision of an improved apixaban formulation. Further references to the bioavailability, immediate release or consistency of exposure were to be avoided, because they included impermissible pointers to the solution, which was based on the finding that the exposure from 5 mg apixaban tablets is affected by the dissolution rate as

disclosed for the first time in the original application for the patent.

Document D1 provided no suggestion towards the claimed solution aimed at the enhanced dissolution of crystalline apixaban in an IR formulation. On the contrary, document D1 disclosed solid amorphous dispersions of apixaban as solubility improved forms for use in controlled release formulations and thus taught away from the crystalline apixaban and its formulation into an IR tablet as defined in claim 1 of the main request.

As indicated in the declarations in documents D115, D121 and D143 by Prof. Blume the skilled person had furthermore no motivation to seek enhanced dissolution of apixaban in an IR tablet containing only 5 mg apixaban. At a dose of 5 mg apixaban qualified according to the Biopharmaceutical Classification System (BCS) as a class III compound, which implied that its bioavailability was not expected to depend on its dissolution, but only on its absorption. As explained in the declaration by Prof. Davies in document A154 any reservations in the context of the BCS as to the dissolution rates of class III drugs did not concern the skilled person's expectations in the original development of an IR tablet, but addressed the eligibility for waivers for *in vivo* bioavailability and bioequivalence studies, the so-called "biowaivers", for subsequent market authorizations.

As indicated by the declaration by Prof. Myerson in document D142 and by Prof. Davies in document A154 the skilled person was also well aware of the

disadvantages of a reduced particle size of active ingredients and the availability of alternatives measures for enhancing the dissolution rate. The skilled person would therefore not seek to develop an IR tablet comprising crystalline apixaban with a reduced particle size, especially if the prior art provided no motivation for the reduced particle size and actually tought away from such tablets.

Document D2 described a process for transforming a first polymorph of a chemical agent into a second polymorph of the same agent involving a particular apparatus and specific process steps. Document D2 presented examples of this process involving apixaban. Faced with the objective technical problem starting from document D1 the skilled person had no motivation to consider the teaching of document D2, because the teaching in document D1 concerned controlled release formations and solid amorphous dispersions of apixaban. Moreover, document D2 did not refer to any particular dose of apixaban in a pharmaceutical formulation and was therefore of no relevance to the claimed subject-matter which involved a tablet comprising a dose of apixaban at which its bioavailability could not be expected to be influenced by its dissolution.

Documents D116-D118 demonstrated that the claims covered a successful pharmaceutical product, namely Eliquis(R), which represented a secondary indication that the claimed subject-matter involved an inventive step.

The core disclosure of document D1 was directed to controlled release formations and solid amorphous dispersions of apixaban. In accordance with the

established jurisprudence as represented by T 56/87, T 414/98, T 501/04, T 776/96, T 297/91 and T 177/98 the entirety of the closest prior art teaching needed to be taken into consideration when assessing inventive step. If the Board intended to decide that the claimed IR tablets comprising crystalline apixaban were nevertheless obvious in view of document D1 as closest prior art, it should refer the following question to the Enlarged Board of Appeal:

"Is it allowable in the assessment of non-obviousness starting from a comparative example as the closest prior art within a pre-published document to isolate this comparative example from the entirety of the teaching of this document in order to derive from the prior art document a technical information which is limited to the disclosure of the comparative example and, thus, distinct from the entirety of the teaching of this document?"

(c) Auxiliary requests

Auxiliary requests 1-2 complied with the requirement of inventive step for the same reasons as the main request.

Auxiliary request 3 additionally defined the composition for use in the treatment of a thromboembolic disorder. The effective treatment implied by this feature further distinguished the claimed subject-matter from the teaching of document D1, which did not describe the IR tablet of example 7 for the purpose of effective treatment of thromboembolic disorders, but only for use in

experiments with healthy subjects as comparative formulation with respect to the controlled release formulations actually intended for therapeutic treatment in accordance with document D1. Document D1 provided no suggestion towards the claimed modified IR tablets as solution to the problem of providing an improved apixaban formulation for the effective treatment of a thromboembolic disorder.

XII. The arguments of the opponents relevant to the present decision are summarised as follows:

(a) Admittance of documents filed during the appeal proceedings

Document A157 was filed in response to the filing of document A154. Document A155 related to the decision from the UK High Court denying that the patent involved an inventive step in view of document A156. Document A155 provided a relevant opinion regarding the common knowledge which was in agreement with the declaration in document A157. Documents A155-A157 should therefore be admitted.

Documents A152-A154 were not to be admitted for being late filed without justification and lacking relevance. Documents A159 and A160 lacked relevance, because they concerned, like documents D140 and D141, decisions from jurisdictions which do not apply the EPC and EPO case law and did not provide further information relevant to the appeal proceedings.

The Board should further not take the patent proprietors' submissions of 22 December 2023 into account, because these submissions were repetitive

and failed to address the Board's decision in T 702/22 regarding the revocation of EP3246021, which concerned essentially the same issues as the present appeal.

(b) Main request

Document D1 disclosed pharmacokinetic data (Table 1) and ingredients (Table 8) of the IR tablet of example 7 which were similar to the data and components disclosed for the tablets in the patent (see Table 6 and Table 3). From the content of document D1 as a whole, including the references to control compositions with crystalline apixaban, it was evident that crystalline apixaban was used for the IR tablet of comparative example 7. Consequently, the particle size and dissolution rate of the IR tablet of example 7 in document D1 had to be within the range defined in claim 1 of the main request. Moreover, the defined dissolution profile concerned a result to be achieved and the process features defined in the claim, including the defined D_{90} value for the starting material, did not give rise to a distinct and identifiable characteristic of the claimed product. These features were therefore unsuitable to distinguish the defined subject-matter from the composition of the prior art.

The experimental results relied upon by the appellants were not indicative of any effect from any new feature of the claimed formulation with respect to the IR-tablet of example 7 in document D1. On the contrary, document D1 described for this tablet similar pharmacokinetic characteristics.

In as far as the available results were nevertheless considered to demonstrate that some new feature of the claimed formulations was associated with the effect of consistent solution-like bioavailability of the apixaban and the objective technical problem could in view of the known IR tablet of document D1 be formulated as the provision of an IR tablet with optimized properties, the claimed solution did not involve an inventive step.

The reduction of the particle size of active ingredients was an established method for improving dissolution characteristics and thereby the bioavailability of active agents in IR formulations. This common general knowledge was reflected in document D2, which described the preparation of crystalline apixaban with a reduced particle size. The skilled person, who was aware of the problematic solubility of apixaban from document D1 itself, would therefore in view of the teaching of document D2 or even just the common general knowledge by itself provide apixaban in a crystalline form with a reduced particle size and secure its rapid dissolution as defined in claim 1 of the main request to arrive at the claimed solution in an obvious manner.

As explained in the declaration by Prof. Frieß in document D145 and the declaration by Dr Stott in document A157, the expectation that the bioavailability of a BSC class III drug depends on its absorption rate and not on its solubility was subject to the reservation that the drug has an adequate dissolution rate. This reservation did not exclusively concern the eligibility of generic

drugs for biowaivers for subsequent market authorizations.

Known potential disadvantages of particle size reduction were not addressed in the patent and could not withhold the skilled person from applying this well established method to optimize the dissolution characteristics of crystalline apixaban.

Whilst document D1 described solid amorphous dispersions of apixaban in controlled release formations as solution to the problem of providing apixaban formulations for once daily administration, the document disclosed the IR tablet of comparative example 7 as a viable dosage form in its own right. The skilled person would therefore, in line with the considerations in T1711/16 as well as T 56/87, T 414/98, T 501/04, T 776/96, T 297/91 and T 177/98 regard this IR tablet as a suitable starting point in the prior art and consider its further development to the tablet of claim 1 of the main request obvious taking account of the disclosure of document D1 in its entirety. The patent proprietors' request for a referral to the Enlarged Board of Appeal was therefore to be rejected.

(c) Auxiliary requests

Auxiliary requests 1-2 did not comply with the requirement of inventive step for the same reasons as the main request.

The same objection also applied with respect to auxiliary request 3. Document D1 already described

the IR tablet of example 7 to provide suitable bioavailability. The patent did not provide any evidence relevant to effective treatment that went beyond the bioavailability of the apixaban following the administration of the claimed tablets. Effective treatment of a thromboembolic disorder from twice daily administration of conventional tablets with 5 mg apixaban had in fact already been reported in document D133.

XIII. The patent proprietors (appellants) requested that the decision under appeal be set aside and that the patent be maintained on the basis the main request or one of auxiliary requests 1-3, all filed with the statement of grounds of appeal, corresponding to auxiliary requests 1, 3, 5 and 7 on which the decision under appeal was based.

The patent proprietors further requested that documents D140-D141, A152-A154 and A159-A160 be admitted and that documents A155-A158 and the third party observations not be admitted into the appeal proceedings.

The patent proprietors also requested, conditionally, that the following question be referred to the Enlarged Board of Appeal:

"Is it allowable in the assessment of non-obviousness starting from a comparative example as the closest prior art within a pre-published document to isolate this comparative example from the entirety of the teaching of this document in order to derive from the prior art document a technical information which is limited to the disclosure of the comparative example and, thus,

distinct from the entirety of the teaching of this document?"

XIV. The opponents (respondents) requested that the appeal be dismissed.

The opponents further requested that documents D140-D141, A152-A154 and A159-A160 not be admitted into the appeal proceedings and that the request for referral to the Enlarged Board of Appeal be refused.

Opponent 1 further requested that the Board conducts an analysis of inventive step from both the priority and the filing dates. Opponent 1 also requested that the patent proprietors' submission of 22 December 2023 not be taken into account.

Reasons for the Decision

Admittance of documents and submissions filed during the appeal proceedings

1. In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that documents D140, D141, A152-155, A157, A159 and A160 were to be admitted and that documents A156 and A158 and the third party observations were not to be admitted.

No substantive arguments regarding the admittance of these documents were subsequently presented by the parties.

The Board has therefore confirmed its preliminary opinion and has admitted documents D140, D141, A152-155, A157, A159 and A160, and not admitted

documents A156 and A158 and the third party observations into the appeal proceedings.

The allegedly repetitive nature of the patent proprietors' submission of 22 December 2023 and the circumstance that this submission does not address the Board's decision in T 702/22 regarding the revocation of EP3246021, which was announced at the end of the oral proceedings held on 21 December 2023, do not in anyway represent a ground for not taking the submission of 22 December 2023 into consideration, as requested by opponent 1.

Main request

2. Priority

According to the decision under appeal the claims of the main request do not enjoy the claimed priority, because the priority document does not disclose the feature of the apixaban particles having a D_{90} of less than 89 µm.

The patent proprietors did not contest this finding in the decision under appeal.

Document D1, which was published after the priority but before the filing date, is therefore regarded as prior art under Article 54(2) EPC.

3. Novelty

3.1 Document D1 discloses modified release formulations comprising apixaban in a solubility-improved form which may allow for the effective once daily administration of apixaban (see for instance D1, page 12, lines

24-32). Document D1 also describes in example 7 an immediate release (IR) tablet containing 5 mg apixaban (see D1, page 73). Document D1 discloses the preparation of this IR tablet by a dry granulation process using the same excipients in similar relative amounts as described in the patent for the preparation of apixaban tablets via dry granulation (see D1, page 73, Table 8; see the patent, page 6, Table 3). Document D1 further describes a crossover study with healthy subjects in which the IR tablets of example 7 were used as control for comparison with modified release tablets (see D1, pages 63-66). The presented pharmacokinetic data from this study indicate for a double dose of the 5 mg IR apixaban tablets of example 7 a C_{max} and AUC_{inf} (183 ng/ml, 2035 ng*hr/ml), which could be considered to correlate with the C_{max} and AUC_{inf} (108.3 ng/ml, 1153 ng*hr/ml) mentioned in the patent for a double dose of the 2.5 mg apixaban tablets obtained by dry granulation process (see D1, page 65, Table 1; see the patent, page 8, Table 6).

3.2 Document D1 does not explicitly disclose the IR tablets of example 7 to contain apixaban in crystalline form (see D1, page 73, Table 8).

Document D1 mentions that dosing apixaban in solubility-improved form provides for a favourable AUC with 1.25-fold to 20-fold bioavailability relative to a control composition consisting of an equivalent quantity of apixaban in bulk crystalline form. In this context document D1 indicates that the relative bioavailability can be determined in an *in vivo* test such as a crossover study involving a control composition "as described above" and describes the set-up of such a crossover study involving "a control

composition that consist of an equivalent quantity of crystalline apixaban" (see D1, page 40, lines 5-32).

However, it cannot be concluded from the generic description of a crossover study intended to demonstrate *in vivo* the favourable AUC of solubility-improved apixaban with respect to a control composition with crystalline apixaban (see D1, page 40) that in the subsequently described crossover study, which involved modified release tablets comprising solubility-improved apixaban and the IR tablets of example 7 as control, these control composition must also have included crystalline apixaban. In fact, this subsequent crossover study showed for the solubility-improved apixaban in the modified release tablets a reduced AUC as compared to the apixaban in the IR tablet of example 7 (see D1, page 64, lines 23-25).

Document D1 further refers to *in vitro* dissolution tests to demonstrate the improved solubility of solid amorphous dispersions of apixaban in comparison to crystalline apixaban used as control (see D1, pages 39, 49, 67-68 and 72-73). However, the use of crystalline apixaban *per se* as control in such *in vitro* dissolution tests does also not allow for the conclusion that the IR tablet of example 7 used as control in the mentioned *in vivo* crossover study necessarily included crystalline apixaban.

The Board therefore considers that it cannot be directly and unambiguously derived from document D1 that the IR tablet of example 7 contained apixaban in crystalline form.

3.3 Document D1 describes with respect to the dissolution properties merely that "immediate release" means that

at least 70% of the initially present compound is released within one hour or less (see D1, page 5, lines 10-15). Document D1 provides no information regarding the particle size of the apixaban used to prepare the IR tablets of example 7.

The argument that the features of the dissolution profile and the particle size could not distinguish the defined subject-matter from the prior art, because the defined dissolution profile concerns a result to be achieved and because the process features in the claim, including the defined D_{90} value for the starting material, would not give rise to a distinct and identifiable characteristic of the claimed product, is not considered convincing.

It is not evident that the preparation of the tablets using a dry granulation process should significantly affect the particle size of the crystalline apixaban. The opponents have not presented any evidence in this respect. The Board therefore agrees with the finding in the decision under appeal (see pages 35-36, bridging section), that the skilled person understands that the defined tablet preparation results in a characteristic internal structure of the tablets owing to the defined particle size of the crystalline apixaban.

The defined dissolution profile of the apixaban represents undisputably a determinable feature of the claimed tablet which is *inter alia* affected by the solid state form and the particle size of the apixaban used to prepare the tablets. Such a determinable feature cannot simply be ignored when comparing the claimed subject-matter with the prior art.

The Board further observes that at the relevant date the content of the patent was not available to deduce from the pharmacokinetic data in document D1 that the IR tablet of example 7 must have comprised apixaban in the form as defined for the tablets in claim 1 of the main request and should therefore display a corresponding dissolution profile of the apixaban.

The Board therefore considers that document D1 does not disclose a particle size of the apixaban used for the IR tablets of example 7 nor a dissolution rate of the apixaban from these tablets corresponding to the definition in claim 1 of the main request.

3.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the main request is new over example 7 of document D1.

4. Inventive step

4.1 Closest prior art

It was not in dispute that the IR tablet of example 7 of document D1 qualifies as suitable starting point in the prior art.

As explained in section 3 above the Board considers that the tablet as defined in claim 1 of the main request differs from the tablets of example 7 of document D1 in the following features:

- the crystalline form of the apixaban

- the particle size distribution of the apixaban

- the dissolution profile of the apixaban from the tablet.

4.2 Objective technical problem

The patent presents in paragraphs [0038] and [0039]a discussion of the experiments for which the results are presented in Tables 6 and 6a and Figures 1-4. In this discussion the patent informs that based on the results of the described experiments solution-like bioavailability may be expected statistically with 90% confidence for tablets with a dissolution rate of at least 77% in 30 minutes and that such dissolution may be achieved with tablets containing 5 mg apixaban with a D_{90} below 89 µm. The explanations in documents D112 and A152 confirm this information.

A direct comparison with the tablet of example 7 in document D1 is precluded due to the absence of definitive information in document D1 regarding the solid state form, the dissolution profile and the particle size of the apixaban used for that tablet. However, in view of the absence of information regarding the exact constitution of the tablet of the prior art the Board considers that taking account of the above mentioned solution-like bioavailability of the claimed tablets the objective technical problem may still be seen in the provision of an optimized tablet for immediate release of apixaban.

In this context the Board rejects the suggestion by the patent proprietors that this formulation of the objective technical problem includes an impermissible pointer to the solution by anticipating that the improved tablet is a tablet for the immediate release of apixaban. Pointers to the solution implied by the

differences with the starting point in the prior art, in particular the dissolution profile of the apixaban in the tablet, are indeed to be avoided in the formulation of the objective technical problem. However the objective of providing an optimized tablet for immediate release of apixaban does not include any pointer to a difference with the starting point in the prior art, because document D1 already discloses in example 7 a tablet for immediate release of apixaban.

The circumstance that document D1 is concerned with the development of apixaban formulations which provide sustained release of a solubility-improved form of apixaban aimed at once daily administration and discloses the IR tablet of example 7 as a comparative example in a bioavailability study involving healthy subjects, does not detract from the fact that the IR tablet of example 7 used as a control composition is described as a viable dosage form in its own right allowing for high bioavailability following oral administration (see D1, page 64, lines 23-25). In line with the considerations in T 1711/16 (see Reasons 7.5) the skilled person would therefore take up the IR tablet of example 7 with the objective of its further development, including its optimisation.

Starting from the IR tablet as described in document D1 the Board therefore considers the provision of an optimized tablet for immediate release of apixaban as a realistic formulation of the objective technical problem which avoids any pointer to the claimed solution.

4.3 Assessment of the solution

4.3.1 Faced with the problem of providing an optimized tablet for immediate release of apixaban starting from example 7 of document D1 the skilled person would be aware of the potentially problematic solubility of apixaban from document D1 itself, which indicates that apixaban has a low solubility in aqueous environments and that solubility-improved forms allow for enhanced drug concentrations in gastrointestinal fluid (see D1, page 31, lines 1-8).

In view of the potentially problematic solubility of apixaban the skilled person would be motivated to address the dissolution characteristics of apixaban for the purpose of providing an optimized tablet for the immediate release of apixaban.

In this context the skilled person would on the basis of his common general knowledge (see for instance D135) be aware of the Biopharmaceutical Classification System (BCS). The BSC categorises drugs in four classes according to their dose weighted water solubility and membrane permeability, which broadly allows the prediction of the rate-limiting step for absorption following oral administration and the effect of the formulation of a drug on its oral bioavailability. The BSC is used in the context of drug discovery and development as well as in drug approval procedures (see D135, abstract and page 740, right column).

A compound with a high water solubility in relation to its dose strength and a low membrane permeability is categorized as a BSC class III drug. For BSC class III drugs the permeability is generally predicted as the rate-limiting factor in absorption rather than dosage

form factors which affect the dissolution (see D135, page 741, right hand column). In view of the solubility of apixaban of 40 µg/ml at relevant conditions reported in the patent (paragraph [0005], see also D78, pdf-page 17) apixaban may qualify at a dose of 5 mg as such a BCS class III drug. According to the patent proprietors the skilled person would therefore not have expected that the dissolution rate of apixaban, as a BCS class III drug, would have affected its absorption and would thus not have considered measures aimed at increasing apixaban's dissolution rate in order to optimize the IR tablet of document D1.

However, the literature cited in the appeal proceedings regarding predictions for oral bioavailability based on the BCS, in particular BCS class III drugs, consistently maintains a reservation with respect to the sufficiently rapid dissolution rate of the drug concerned, namely that the permeability of the active pharmaceutical ingredient is expected to be the rate controlling step of the absorption only if the dosage form dissolves rapidly:

> see document D8, page 923, left column: "If the dissolution of Class III products is rapid under all physiological pH conditions, it can be expected that they will behave like an oral solution *in vivo*."; see also page 923, right column: "To minimize the possibility of dissolution behaviour anomalies (...) it would be necessary to set a more rapid *in vitro* dissolution rate criterion of no less than 85% within 15 min for Class III drugs"
>
> see document D18, page 119, right column: "If their dissolution is rapid under all physiological pH conditions, it can be expected that they will also

behave like an oral solution *in vivo*"; see also page 118, right column: "Consequently, additional requirements on dissolution behaviour were introduced in the system. Thus, a waiver of bioavailability studies may only be granted for products whereby more than 85% of the drug ingredient is dissolved in 30 min in all physiological media."

see document D4, page 417, right column: "if dissolution is fast, i.e. 85% dissolved in less than 15 min. this variation will be due to gastrointestinal transit (...) rather than dosage form factors"

see document D10, page 2 :"In addition, IR solid oral dosage forms are categorized as having rapid or slow dissolution. Within this framework, when certain criteria are met, the BCS can be used as a drug development tool (...)"; see also pages 2-3, bridging sentence: "an IR drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes (...)"

see document D58, page 1243, right column: "Therefore, biowaivers for BCS class 3 drug products with suitably rapid dissolution..."; see also page 1236, right column: "both the WHO and the EMA extend biowaivers to some class III drug compounds when they meet the criterion for very rapid dissolution drugs (>85% solubility at pH 1,2-6.8 in 15 min)"

see document D7, page 25/27: "BCS-based biowaver are also applicable for an immediate release drug

product if the drug has (...) very rapid (85% within 15 minutes *in vitro)* dissolution (...)"

see document D74, page 3, lines 2-5: "The BCS suggests that for (...) (case 3) drugs, 85% dissolution in 0.1 N HCl in 15 minutes can ensure that the bioavailability of the drug is not limited by dissolution."

see document D9, page 307, right column: "For Class III compounds that are rapidly dissolving (...) a new formulation may be considered acceptable if both the new and old formulations are more than 85% dissolved in 15 min (...)"

see document D104, page 1380, left column: "a more rapid dissolution requirement of at least 85% dissolved in 15 min is an important requirement in order to extend biowaivers to Class 3 drugs."

see document D135, page 741, right column: "An IR product is characterized as rapidly dissolved if not less than 85% of the labeled drug amount is dissolved within 30 min" and "If the *in vitro* dissolution of Class III drug is rapid under all physiological pH conditions, its *in vivo* behaviour will essentially be similar to oral solution (...)"

see document A153, page 209, right column: "Unter der Annahme, dass insbesondere (...) die Löslichkeit und die Fähigkeit, die Intestinalmembranen zu permeieren, für die Bioverfügbarkeit entscheidend sind, wurde as Biopharmazeutische Klassifizierungssystem (...) entwickelt" [translation by the Board: "Assuming that in particular (...) the solubility and the

ability to permeate the intestinal membranes are crucial for bioavailability, the Biopharmaceutical Classification System (...) was developed"]; see also page 215, right column: "Daher ist die Bestimmung der Lösungsgeschwindigkeit eins der wichtigsten Bestimmungsverfahren im Rahmen der Qualitätskontrolle" [translation by the Board: "Therefore, the determination of the dissolution rate is one of the most important determination procedures in the context of quality control"]

This reservation is further in line with the biopharmaceutical classification of drugs based on the intrinsic dissolution rate as proposed in document D149 (see page 105, left column) as well as with the common general knowledge that the particle size of a drug may affect its bioavailability, if the drug's absorption is limited by its dissolution rate (see D17, page 2703, left column; D38, page 335; D49, page 11; D84, page 5; D94, page 288, left column).

Notably, the above cited passages from the literature concerning predictions for oral bioavailability of BCS class III drugs qualify the dissolution of a drug as rapid, if at least 85% of the drug dissolves within 30 minutes or even more stringently within 15 minutes. At the same time these passages underline the importance of such rapid dissolution for the assumption that a composition with such a rapidly dissolving drug will behave *in vivo* essentially similar to an oral solution or the assumption that different formulations of a drug will show bioequivalence. Such assumptions are not only relevant for granting "biowaivers", which represent permission to proceed with clinical studies for obtaining regulatory approval using different formulations without showing bioequivalence of the

formulations on the basis of *in vivo* studies (see document A154, page 5, lines 6-10), but also in the original development of an IR tablet of a drug, because solution-like in vivo behaviour corresponds to optimal performance of an immediate release formulation.

The Board therefore considers that in addressing the problem of providing an optimized tablet for immediate release of apixaban starting from example 7 of document D1 the skilled person would take up measures to secure the rapid apixaban dissolution and in particular aim for a dissolution of 85% within at least 30 minutes for optimizing the IR tablet of example 7 of document D1.

4.3.2 It was not in dispute that the reduction of the particle size of pharmaceutically active agents was a well established method for improving the dissolution characteristics of the active agents in immediate release formulations.

Document D2 refers to this common general knowledge stating that the bioavailability of a sparingly soluble organic compound is often enhanced when the agent is in pure from and has a small and uniform particle size with a high surface area and short dissolution time (see D2, paragraph [0003]). In this context document D2 recognizes the need for a robust crystallization process for providing small and uniform crystals with high purity, stability and surface area without the necessity of post-crystallisation milling (see D2, paragraph [0011]). To address this need document D2 discloses a process for transforming a polymorph form with large crystals in a polymorph form with small crystals (see D2, paragraphs [0012] and [0020]). Document D2 presents examples of the disclosed process involving apixaban in which large needle-shaped

crystals are transformed into small, granular crystals having a D_{90} particle size of less than 20 µm (see D2, Examples 1-3).

In view of the described purpose of the process in document D2, namely the provision of crystals of a small uniform particle size with high purity, high stability and high surface area, which in line with the mentioned common general knowledge results in an enhanced dissolution rate, the skilled person who intends to prepare an optimized IR tablet for apixaban by securing at 85% apixaban dissolution within at least 30 minutes, would take account of the teaching document D2 and use the crystalline apixaban having a particle size D_{90} of less than 20 µm as described in the examples of document D2.

Accordingly, the skilled person would arrive at the subject-matter of claim 1 of the main request in an obvious manner.

4.3.3 The patent proprietors argued, that the core teaching of document D1 was concerned with the development of sustained release formulations of a solubility improved amorphous form of apixaban. In their view the skilled person would therefore not have modified the IR tablet to provide an optimized IR tablet, let alone an optimized tablet with crystalline apixaban, because this would go against the teaching of document D1 when considered in its entirety. In this context the patent proprietors referred to the established jurisprudence, according to which the entirety of the closest prior art teaching was to be taken into account in the assessment of inventive step.

According to the established jurisprudence the technical disclosure in a prior art document has to be considered in its entirety, as it would be done by a skilled person, and it is not justified to arbitrarily isolate parts of such document from their context in order to derive therefrom a technical information which would be distinct from or even in contradiction with the integral teaching of the document (see Case Law of the Boards of Appeal of the EPO, 10th ed., I.D.9.5, see in particular T 56/87 (see under "Novelty", reasons 3.1), T 414/98 (reasons 6.1-6.2), T 501/04 (reasons 2.5), T 776/96 (reasons 5.3), T 297/91 (reasons 9.1-9.2) and T 177/98 (reasons 2.5.1).

The Board considers that in line with this jurisprudence the reasons for denying that the claimed subject-matter involves an inventive step set out above take account of the technical disclosure of document D1 in its entirety and avoid any arbitrary isolation of the disclosure of the control IR tablet of example 7 to derive any technical information which would be distinct from or even in contradiction with the integral teaching of the document.

In particular, the Board's reasons identify within the entirety of the teaching in document D1 the IR tablet of example 7 as a viable dosage form in its own right taking account of the bioavailability following oral administration of this comparative composition described in document D1 (see section 4.2 above). Whilst it would go against the teaching of document D1 to modify the sustained release formulations to obtain dissolution properties as claimed in the opposed patent, this is not the case for the tablet of example 7, which according to document D1 is aimed at the immediate release of apixaban. The Board further

observes that document D1 describes the solid amorphous dispersion of apixaban as a preferred example of a solubility-improved form of apixaban for incorporation in the described controlled release formulations, but also mentions other solubility-improved forms of apixabann to be suitable, including crystalline highly soluble forms (see D1, pages 2-3, bridging section; see also page 37). Document D1 does thereby not generally teach away from crystalline apixaban, let alone from the pure crystals of apixaban having a small uniform particle size with high purity, high stability and high surface area described in document D2.

The patent proprietors' argument relying on the teaching of document D1 as teaching away from the claimed subject-matter when considered in its entirety is therefore not considered convincing.

4.3.4 The patent proprietors' argument relying on the declarations in documents documents D115, D121, D143 and A154 that the enhanced dissolution of apixaban from a formulation with a 5 mg dose was not expected to have any effect on the bioavailability of the apixaban, because at such dose the apixaban is to be regarded as a BCS class III drug is also not considered convincing.

As explained in section 4.3.1 above, the expectations concerning the bioavailability of a 5 mg dose of apixaban as a BCS class III drug are subject to the reservation that the dissolution rate of the drug is sufficiently rapid.

In contrast to the declarations in documents D145 and A157 relied upon by the opponents the declarations in documents D115, D121, D143 and A154 relied upon by the

patent proprietors do not seem to take due account of this reservation.

4.3.5 The patent proprietors further argued, that the skilled person would not consider the teaching of D2 for solving the objective technical problem starting from document D1, because document D2 relates to a process for transforming a first polymorph of a chemical agent into a second polymorph of the same agent, whereas the teaching in document D1 focuses on controlled release formations and solid amorphous dispersions, and because document D2 did not mention any particular dose of apixaban in a pharmaceutical formulation and was therefore of no relevance to the claimed subject-matter which involved a tablet comprising a dose of apixaban at which it qualified as a BCS class III drug.

This argument is not convincing, because it fails to acknowledge on the one hand that document D1 describes the IR tablet of example 7 as a viable dosage form in its own right and does not at all teach away from crystalline apixaban and on the other hand that document D2 describes a process for preparing apixaban having a small uniform particle size with high purity, high stability and high surface area, which in accordance with the common general knowledge specifically cited in document D2 may be expected to allow for enhanced bioavailability.

4.3.6 The patent proprietors' further argument, that the skilled person would in view of the potential disadvantages of a reduced particle size of active ingredients and the availability of alternatives for enhancing the dissolution rate not seek to develop an IR tablet comprising crystalline apixaban with a

reduced particle size, is also not considered convincing.

The argument regarding the disadvantages of a reduced particle size had been rejected in the decision under appeal (see section 10.4.3.3), because the skilled person would tolerate known potential disadvantages of a feature, if the interest in the advantage of the feature prevails, and because it had not been indicated how the claimed compositions would overcome the alleged disadvantages. Taking account of the common general knowledge regarding particle size reduction as a conventional method to achieve *inter alia* enhanced dissolution of drugs as well as the actual availability of apixaban having a small uniform particle size with high purity, high stability and high surface area from the process described in document D2 the Board agrees with the finding in the decision under appeal.

The Board further considers that the availability of alternative methods for improving the dissolution rate of apixaban does not distract the skilled person from applying the conventional method of particle size reduction to enhance the dissolution of apixaban from an IR tablet.

4.3.7 According to the decision under appeal (see section 10.4.3.6) the evidence regarding the success of the product Eliquis(R) as reported in documents D116-D118 did not allow for the conclusion that this success was due to the distinguishing features of the claimed subject-matter with respect to the closest prior art. The Board agrees and therefore considers that the success of the product Eliquis(R) does not affect the finding that the claimed subject-matter lacks an inventive step.

4.4 Accordingly, the Board concludes that the subject-matter of claim 1 of the main request does not involve an inventive step.

5. Request for referral to the Enlarged Board of Appeal

5.1 In case the Board intended to decide that the claimed IR tablets comprising crystalline apixaban was obvious in view of document D1 as closest prior art, the patent proprietors requested that in the light of the established jurisprudence as represented by T 56/87, T 414/98, T 501/04, T 776/96, T 297/91 and T 177/98 the Board referred the following question to the Enlarged Board of Appeal:

"Is it allowable in the assessment of non-obviousness starting from a comparative example as the closest prior art within a pre-published document to isolate this comparative example from the entirety of the teaching of this document in order to derive from the prior art document a technical information which is limited to the disclosure of the comparative example and, thus, distinct from the entirety of the teaching of this document?"

5.2 As explained in section 4.3.3 above, the Board considers that in line with principles established in the cited jurisprudence the reasons for denying that the subject-matter of claim 1 of the main request lacks an inventive step in view of document D1 as closest prior art take account of the technical disclosure of document D1 in its entirety and avoid any arbitrary isolation of the disclosure of the control IR tablet of example 7 to derive any technical information which

would be distinct from or even in contradiction with the integral teaching of the document.

The Board does therefore not consider it necessary in view of Article 112(1) EPC to refer the question formulated by the patent proprietors to the Enlarged Board of Appeal.

Auxiliary requests

6. Auxiliary requests 1-2 (inventive step)

Claim 1 of auxiliary request 1 is identical to claim 1 of the main request. Auxiliary request 1 does therefore not meet the requirement of inventive step for the same reasons as set out for the main request.

The additional definition of the conditions for the dissolution test in claim 1 of auxiliary request 2, according to which the dissolution test is performed in 900 ml of dissolution medium containing 0.05 M sodium phosphate at pH 6.8 with 0.05% SDS at 37 °C using USP Apparatus 2 (paddles) at a rotation speed of 75 rpm and the samples are analyzed for apixaban by HPLC at 280 nm, seem conventional for establishing the rate of dissolution of a drug (see D1, page 11, lines 14-29). No particular effect on the performance of the defined tablet has been demonstrated to be associated with these defined conditions. The additional features in claim 1 of auxiliary request 2 do therefore not materially effect the Board's reasons for denying an inventive step for the subject-matter of claim 1 of the main request. Accordingly, auxiliary request 2 is also not considered to meet the requirement of inventive step.

7. Auxiliary requests 3 (inventive step)

The additional feature in auxiliary request 3 with respect to auxiliary request 2, that the tablet is for use in the treatment of a thromboembolic disorder, corresponds with the known indication for apixaban already mentioned in document D1 in the section "Background of the invention" (see D1, pages 1-2). Concerning the effectiveness of the treatment implied by these features the Board further observes that the patent does not provide any evidence that goes beyond the bioavailability of the apixaban following the administration of the claimed tablets as already reported in document D1. This features does thus not relate to any effective technical contribution over the prior art.

The additional feature in auxiliary request 3 does therefore not overcome the objection of lack of inventive step against the subject-matter of claim 1 of auxiliary request 2. Accordingly, auxiliary request 3 does also not meet the requirement of inventive step.

Request for assessment of inventive step as from the priority date

8. Following the conclusion that the main request and auxiliary requests 1-3 do not meet the requirement of inventive step in view of document D1 as closest prior art any further assessment on the basis of the state of the art at the priority date would not affect the outcome of the appeal. The Board therefore rejects the request for such assessment.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The request for referral to the Enlarged Board of Appeal is refused.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated