Internal distribution code:

(A) [-] Publication in OJ
(B) [-] To Chairmen and Members
(C) [-] To Chairmen
(D) [X] No distribution

Datasheet for the decision of 1 February 2024

Case Number: T 2163/22 - 3.3.07

Application Number: 17178613.0

Publication Number: 3257500

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:
ZAKLADY FARMACEUTYCZNE POLPHARMA S.A.
Kutzenberger Wolff & Partner
Zentiva k.s.
Medichem S.A.
Teva Pharmaceutical Industries Ltd
Sandoz AG
Generics (U.K.) Limited
STADA Arzneimittel AG

Headword:
Apixaban IV/Bristol-Myers

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

Keyword:
Novelty - (no)
Inventive step - (no) - comparative example suitable starting point for assing 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, T 0032/17, T 0205/83, T 0564/02

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0
Fax +49 (0)89 2399-4465

Case Number: T 2163/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 1 February 2024

Appellant: (Patent Proprietor 1)	Bristol-Myers Squibb Holdings Ireland Unlimited Company Hinterbergstrasse 16 6312 Steinhausen (CH)
Appellant: (Patent Proprietor 2)	Pfizer Inc. 235 East 42nd Street New York, NY 10017 (US)
Representative:	Uexküll & Stolberg Partnerschaft von Patent- und Rechtsanwälten mbB Beselerstraße 4 22607 Hamburg (DE)
Respondent: (Opponent 1)	ZAKLADY FARMACEUTYCZNE POLPHARMA S.A. ul. Pelplinska 19 83-200 Starogard Gdanski (PL)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent 2)	Kutzenberger Wolff & Partner Waidmarkt 11 50676 Köln (DE)
Representative:	Kutzenberger Wolff & Partner Waidmarkt 11 50676 Köln (DE)
Respondent: (Opponent 3)	Zentiva k.s. U kabelovny 130 10237 Praha 10 (CZ)

Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 DE-81925 München (DE)
Respondent: (Opponent 4)	Medichem S.A. Avda. Pirineus - Polígon Industrial 17460 Celrà (Girona) (ES)
Representative:	Hamm&Wittkopp Patentanwälte PartmbB Jungfernstieg 38 20354 Hamburg (DE)
Respondent: (Opponent 5)	Teva Pharmaceutical Industries Ltd 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 120 Holborn London EC1N 2DY (GB)
Respondent: (Opponent 8)	Sandoz AG Lichtstrasse 35 4056 Basel (CH)
Representative:	Kraus & Lederer PartGmbB Thomas-Wimmer-Ring 15 80539 München (DE)
Respondent: (Opponent 9)	Generics (U.K.) Limited Building 4, Trident Place Mosquito Way Hatfield Herts AL 10 9UL (GB)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Opponent 10)	STADA Arzneimittel AG Stadastrasse 2-18 61118 Bad Vilbel (DE)
Representative:	Kernebeck, Thomas Kernebeck Patentanwalts GmbH Stiftstraße 2 60313 Frankfurt am Main (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 14 July 2022 revoking European patent No. 3257500 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 3 257 500 ("the patent") was granted on the basis of fifteen claims.

Claim 1 as granted defined a composition for tablets comprising crystalline apixaban having a mean particle size less than 89 µm and a D_{90} less than 89 µm as measured by laser light scattering, wherein the composition comprises up to 5 mg apixaban, a pharmaceutically acceptable diluent or carrier and 0.25 to 2 wt% of a surfactant and the composition is obtainable by a process comprising an air-jet milling process to reduce apixaban particle size and dry granulation.

II. Ten oppositions were originally filed against the grant of 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. Opponents 6 and 7 withdrew their 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 proprietors' main request and auxiliary requests 1-7, which had originally been filed on 16 April 2021 as auxiliary request 1 and auxiliary requests 4-10.

Claim 1 of this main request defined:

"A composition for tablets comprising crystalline apixaban particles having a mean particle size less than 89 µm and a D90 less than 89 µm as measured by laser light scattering, wherein the composition comprises up to 5 mg apixaban, a pharmaceutically acceptable diluent or carrier and a surfactant, wherein the surfactant is present in a concentration of 0.25% to 2% by weight and serves as a wetting aid for apixaban drug substance, wherein the composition is obtainable by a process comprising an air-jet milling process to reduce apixaban particle size to the desired size and dry granulation,
wherein the composition is a tablet which exhibits dissolution properties such that an amount of the drug equivalent to at least 77% dissolves within 30 minutes, wherein the dissolution test is performed in an aqueous media buffered to a pH range 1 to 7.4 and controlled at 37° C, wherein the result is established as an average of 6 tablets."

Claim 1 of auxiliary request 1 defines the conditions for the dissolution test more specifically by the features:

"wherein the result is established as an average of 6 tablets, and 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 requests 2-5 further limit with respect to auxiliary request 1 the amount of apixaban in the tablet as between 2.5 and 5 mg, 2.5 or 5 mg, or 5 mg.

Auxiliary request 6 additionally defines with respect to auxiliary request 5 that the apixaban particles have a D_{90} of less than 25 µm.

Auxiliary request 7 additionally defines with respect to auxiliary request 6 the tablet by the feature:

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

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

D5: US 2006/0160841 A1
D8: WO 2010/147978 A1
D9: Pharmaceutical Research, 1995, 12(3), 413-420
D25: Pharmaceutics: The Science of Dosage Form Design, Aulton, 1988, 1-13, 135-173
D26: Guidance for Industry, Dissolution Testing of Immediate Release Solid Oral Dosage Form, FDA, 1997, 1-11 and A-1/A-2
D32: Clinical Pharmcology and Biopharmaceutics Review, 15 February 2012 (Center for drug evaluation and research, application number 202155Orig1s000)
D38: Pharmaceutical Dosage Forms: Tablets, volume 1, 2nd ed., 1989, 1-24
D40: Molecular Pharmaceutics, 2010, 7(4), 1235-1243
D48: Modern Pharmaceutics, Chapter 10 "Tablet Dosage Forms", Marcel Dekker (G. S. Banker and C. T. Rhodes, Eds., 3rd ed., 1996), 333-359
D61: Pharmaceutics: The Science of Dosage Form Design, Aulton, 3rd ed., 2007, 286-291 and 443-449

D72: European Medicines Agency, Committee for Medicinal Products for Human Use, Guidelines on the investigation of bioequivalence, 2010, pages 1/27-27/27
D74: European Journal of Pharmaceutical Sciences, 1999, 9, 117-121
D75: Pharmaceutical Research, 2002, 9(7), 921-925
D80: Encyclopedia of Pharmaceutical Technology, Volume 3, Marcel Dekker Inc., 2002, Chapter "Tablet Formulation", 2701-2712
D81: The AAPS Journal, 2008, 10(2), 306-310
D82: Journal of Pharmaceutical Sciences, 2004, 93(6), 1375-1381
D88: Guidance for Industry, U.S. Department of Health and Human Services, August 2000,1-13
D93: Declaration of Dr. Jatin Patel, dated 5 May 2017
D96: Expert declaration of Prof. Dr. Henning Blume, dated March 2017
D97: Annual Report 2017 (Form 10-K) of Bristol-Myers Squibb Co.
D98: Husten: "Golden Mean of Anticoagulation", Forbes 28 August 2011
D99: Current Drug Targets, 2012, 13, 863-875
D102: Supplementary expert declaration of Prof. Blume, dated 23 January 2018
D119: Handbook of Powder Technology, Volume 12, Elsevier, 2007, Chapter 8, Air Jet Milling, pages 421-435
D120: Pharmaceutical Extrusion Technology, Marcel Dekker 2003, pages 236-238
D121: Water-Insoluble Drug Formulation, CRC Press, 2008, pages 482-484
D129: Journal of Thrombosis and Haemostasis, 2007, 5, 2368-2375
D142: Decision of the District Court of Delaware, USA, dated 5 August 2020

D143: Decision of the Federal Court of Ottawa, Canada, dated 8 January 2021
D144: Affidavit of Prof. Dr. Allan S. Myerson, dated 22 March 2021
D146: The AAPS Journal, 2009, 11(4), 740-746
D149: Expert declaration of Prof. Dr. Henning Blume, dated 21 March 2021
D152: Expert declaration of Chandra Vema-Varapu, dated 1 December 2021
D154: Lehrbuch der Pharmazeutischen Technologie, Bauer, Kurt H. et al., Stuttgart, Wissenschaftliche Verlagsgesellschaft, 8th ed., 2006, 208-209, 215
D155: Expert Report of Professor Frieß, dated 23 August 2021
D156: Expert Report of Dr Stott, 9 February 2022
D157: Expert Opin. Investig. Drugs, (2008) 17(12), 1937- 1945
D158: Press Release 10 June 2008: "Bristol-Myers Squibb and Pfizer initiate new study in the apixaban Phase 3 clinical trial program"

The opposition division arrived at the following conclusions:

(a) Documents D156-D158 were not admitted into the proceedings.

(b) The main request complied with the requirements of Articles 123(2), 76(1) 84 and 83 EPC.

The subject-matter of the main request did not enjoy the claimed priority. Document D8 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 D8, in particular the tablet of example 7, in view of the defined particle size and the dissolution profile of the apixaban. The process feature that the composition is obtainable by a process comprising air-jet milling did not further characterize the claimed product. The objective technical problem was the provision of an improved apixaban tablet, wherein the improvement was the achievement of consistency of exposure. This problem was credibly solved taking also account of document D152. 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 D5, 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 D8 for essentially the same reasons as explained for the main request.

IV. With their statement of grounds of appeal the patent proprietors upheld the main request and auxiliary requests 1-7 on which the decision under appeal was based.

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

A161: Expert declaration of Prof. Martyn Christopher Davies, 11 July 2022
A162: Decision US Appeal Court of 2021-09-03
A163: Decision CA Federal Court of Appeal of 2022-08-04
A164: Judgment of the UK High Court, [2022] EWHC 1831 (Pat)

Documents A161-A163 were filed by the patent proprietors with the statement of grounds of appeal.

Document A164 was filed by opponents 1, 5 and 9 with their replies to the appeal.

With its reply opponent 5 further re-submitted D156-D158.

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

- documents D156 and A161-A164 were to be admitted, whereas documents D157 and D158 were not to be admitted into the appeal proceedings

- the main request and auxiliary requests 1-7 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 D8.

VII. 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 D8.

VIII. Oral proceedings were held on 1 February 2024.

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

(a) Admittance of documents filed during the appeal proceedings

Document A161 was to be admitted, because it addressed statements in document D155, which had been admitted by the opposition division and relied upon for the finding on the issue of inventive step following its filing on the final date set for written submissions under Rule 116(1) EPC.

Documents A162 and A163 were to be admitted, because these documents related to the appeal decisions confirming the earlier decisions in documents D142 and D143 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 A164 related to a first instance UK decision regarding the patent dealing with the issue of inventive step in view of document D157. Documents D157 and D158 referred to clinical studies involving apixaban, but did not provide any details of apixaban formulations. Document D156 related to a declaration prepared for the UK case and did not represent a response to document A161, which was of a later date. Documents A164 and D156-D158 were thus not pertinent to the appeal proceedings and should therefore not be admitted.

(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 D8 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 as well as the constitution of these particles as a result of the defined size reduction by air-jet milling, which resulted in characteristic surface sections of the particles. Document D144 further explained the effects of milling and document D12A confirmed that the qualifications "milled/not milled" represented characteristic features of a particulate material.

The IR tablet of example 7 of document D8 represented the closest prior art. As confirmed by document D152 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 D8 provided no suggestion towards the claimed solution aimed at the enhanced dissolution of crystalline apixaban in an IR formulation. On the contrary, document D8 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 D96, D102 and D149 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 A161 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 D144 and by Prof. Davies in document A161 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 D5 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 D5 presented examples of this process involving apixaban. Faced with the objective technical problem starting from document D8 the skilled person had no motivation to consider the teaching of document D5, because the teaching in document D8 concerned controlled release formations and solid amorphous dispersions of apixaban. Moreover, document D5 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. Document D5 actually tought away from size reduced particles obtained by air-jet milling by explicitly describing a process for transforming crystals which avoids such post-crystallization milling.

Documents D97-D99 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 D8 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 D8 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 1-6 complied with the requirement of inventive step for the same reasons as the main request.

Auxiliary request 7 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 D8, 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 D8. Document D8 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.

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

(a) Admittance of documents filed during the appeal proceedings

Document D156 was re-submitted in response to the filing of document A161. Document A164 related to the decision from the UK High Court denying that the patent involved an inventive step in view of document D157. Document A164 provided a relevant opinion regarding the common knowledge which was in agreement with the declaration in document D156. Documents D156, D157 and A164 should therefore be admitted.

Documents A162 and A163 lacked relevance, because they concerned, like documents D142 and D143, decisions from jurisdictions which do not apply the EPC and EPO case law and did not provide further information relevant to the appeal proceedings.

(b) Main request

Document D8 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 D8 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 D8 had to be within the range defined in claim 1 of the main request. In line with the established jurisprudence regarding so-called "product-by-process" features as exemplified by T 32/17 the defined size reduction by a jet-milling process was not suitable to further distinguish the defined product, because it was not evident that jet-milling process resulted in a particular distinguishing characteristic of the defined tablet.

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 D8. On the contrary, document D8 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 D8 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 D5, 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 D8 itself, would therefore in view of the teaching of document D5 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.

Air-jet milling was from documents D119-D121 well known as an attractive conventional method to achieve size reduction. Any characteristic of the tablets resulting from the air-jet milling other than the mere size reduction of the apixaban particles would not affect the performance of the tablets and therefore not support an inventive step.

As explained in the declaration by Prof. Frieß in document D155 and the declaration by Dr Stott in document D156, 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 D8 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 D8 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 1-6 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 7. Document D8 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 D129.

XI. 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 1-7 on which the decision under appeal was based, which correspond to auxiliary requests 1 and 4-10 as filed on 16 April 2021.

The patent proprietors further requested that documents A161-A163 be admitted and documents D156-D158 and A164 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?"

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

The opponents further requested that documents D156-D158 and A164 be admitted and documents A161-163 not be admitted into the appeal proceedings.

Opponent 5 further requested that the Board conduct an analysis of inventive step from both the priority and the filing dates.

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 D156 and A161-A164 were to be admitted and that documents D157 and D158 were not to be admitted into the appeal proceedings.

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 D156 and A161-A164, and not admitted documents D157 and D158 into the appeal proceedings.

Main request

2. Priority

According to the decision under appeal (see Reasons, section 8) the claims of the main request do not enjoy the claimed priority, because the priority document does not disclose the features of the apixaban particles having a D_{90} of less than 89 µm, the surfactant in an amount of 0.25 to 2 wt% and the air-jet milling process to produce the apixaban particles.

The patent proprietors did not contest the finding in the decision under appeal regarding the validity of the priority.

Document D8, 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 D8 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 D8, page 12, lines 24-32). Document D8 also describes in example 7 an immediate release (IR) tablet containing 5 mg apixaban (see D8, page 73). Document D8 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 D8, page 73, Table 8; see the patent, page 6, Table 3). Document D8 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 D8, 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 D8, page 65, Table 1; see the patent, page 8, Table 6).

3.2 Document D8 does not explicitly disclose the IR tablets of example 7 to contain apixaban in crystalline form (see D8, page 73, Table 8).

Document D8 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 D8 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 D8, 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 D8, 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 D8, page 64, lines 23-25).

Document D8 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 D8, 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 D8 that the IR tablet of example 7 contained apixaban in crystalline form.

3.3 Document D8 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 D8, page 5, lines 10-15). Document D8 provides furthermore no information regarding the particle size of the apixaban used to prepare the IR tablets of example 7.

The particle size of the apixaban is according to claim 1 measured by laser light scattering. The 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. These features are therefore considered suitable to distinguish of the defined tablet.

The Board observes in this context that at the relevant date the content of the patent was not available to deduce from the pharmacokinetic data in document D8 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 D8 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 D8.

4. Inventive step

4.1 Closest prior art

4.1.1 It was not in dispute that the IR tablet of example 7 of document D8 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 D8 at least 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.

4.1.2 The patent proprietors argued that the feature that the claimed composition is obtainable by a process comprising an air-jet milling process to reduce the apixaban particle size represented a further distinguishing feature.

According to the established jurisprudence such a product-by-process feature only contributes to the novelty of the product insofar it gives rise to a distinct and identifiable characteristic of the product, which may for instance be demonstrated on the basis of conclusive considerations in accord with the general state of the art or distinct differences in the products (see Case Law of the Boards of Appeal of the EPO, 10th Edition 2022, I.C.5.2.7 and II.A.7.2, see in particular T 205/83 (Reasons 3.2.1), T 564/02 (Reasons 3.4 and 3.5) and T 32/17 (Reasons 8)).

The patent proprietors argued in this context that the size reduction by air-jet milling results in a characteristic surface of the apixaban particles and that documents D144 and D12A confirmed the distinctive constitution of particles obtained by milling. The distinctive constitution of the milled particles would according to the patent proprietors be preserved following the compression of the particles into the tablets.

The Board observes that document D144 only refers to specific negative effects that may result from size reduction if milling is used, in particular the occurrence of electrostatic charges, loss of crystallinity, contamination and "dusting" (see D144, page 4). Moreover, document D12A (see page 297, under "Validation") merely indicates in the context of the validation of a method for measuring particle size that "the attainable repeatability of the method mainly depends on the characteristics of the material (milled not milled, robust/fragile width of its size distribution, etc)", without identifying what distinguishes a milled material from non-milled material. Documents D144 and D12A are therefore not considered to actually confirm the distinctive constitution of the apixaban particles obtained by milling. It remains therefore an assertion on behalf of the patent proprietors that the air-jet milling results in a characteristic surface of the particles which is preserved in the final tablets.

4.2 Objective technical problem

The patent presents in paragraphs [0037] and [0038]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 D93 and D152 confirm this information.

A direct comparison with the tablet of example 7 in document D8 is precluded due to the absence of definitive information in document D8 regarding the solid state form, the dissolution profile and the particle size of the apixaban in 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 D8 already discloses in example 7 a tablet for immediate release of apixaban.

The circumstance that document D8 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 D8, 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.

The patent proprietors did not contend that any particular effect on the performance of the final tablets going beyond the effect of the size reduction was associated with the air-jet milling. In the absence of an additional effect from the defined particular method for obtaining the desired particle size on the performance of the claimed tablet the Board considers that any distinction due to the air-jet milling asserted by the patent proprietors is of no relevance in the definition of the objective technical problem.

Starting from the IR tablet as described in document D8 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 D8 the skilled person would be aware of the potentially problematic solubility of apixaban from document D8 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 D8, 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 D146) 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 D146, 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 D146, 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 D32, 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 D8.

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 D75, 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 D74, 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 D9, 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 D88, 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 D40, 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 D72, 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 D26, 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 D81, 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 D82, 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 D146, 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 D154, 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 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 A161, 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 D8 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 D8.

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 D5 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 D5, paragraph [0003]). In this context document D5 states that by slow crystallisation it is possible to obtain a particles of high purity and stability with a large size, which require high intensity milling to create a useable product (see D5, paragraph [0004]).

Document D5 recognized 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 D5, paragraph [0011]). To address this need document D5 discloses a process for transforming a polymorph form with large crystals in a polymorph form with small crystals (see D5, paragraphs [0012] and [0020]). Document D5 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 D5, Examples 1-3). In view of the described purpose of the process in document D5, 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 D5 and use such crystalline apixaban having a particle size D90 of less than 20 µm as described in the examples of document D5. In as far as the assertion by the patent proprietors that the air-jet milling results in a characteristic surface of the particles which is preserved in the final tablets, is incorrect and the air-jet milling does not result in an identifiable characteristic of the defined tablets, the skilled person would thereby arrive at the subject-matter of claim 1 of the main request in an obvious manner.

Even if the patent proprietors are correct in their assertion that air-jet milling results in a characteristic surface of the particles the Board considers that the feature of the composition being obtainable by jet-milling does not contribute to an inventive step. It was common general knowledge in the field of pharmacy that air-jet milling was an attractive method to reduce the size of drug particles and that particle sizes as small as 1-30 µm could thereby be obtained (see D120, page 482, under "Fluid Energy Milling"; see also D119, page 421, under "Introduction" and D121, page 482, under "Fluid Energy Milling"). In view of this common general knowledge it would be obvious to the skilled person who intends provide an optimized IR tablet for apixaban by securing at 85% apixaban dissolution within at least 30 minutes, to subject crystalline apixaban as known from documents D8 or D5 to air-jet milling to obtain the size reduced

crystalline apixaban particles with an enhanced dissolution rate.

4.3.3 The patent proprietors argued, that the core teaching of document D8 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 D8 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 D8 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 D8 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 D8 (see section 4.2 above). Whilst it would go against the teaching of document D8 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 D8 is aimed at the immediate release of apixaban. The Board further observes that document D8 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 D8, pages 2-3, bridging section; see also page 37). Document D8 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 as described in document D5 or otherwise obtained following conventional size reduction, such as by air-jet milling.

The patent proprietors' argument relying on the teaching of document D8 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 D96, D102, D149 and A161 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 D155 and D156 relied upon by the opponents the declarations in documents D96, D102, D149 and A161 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 D5 for solving the objective technical problem starting from document D8, because document D5 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 D8 focuses on controlled release formations and solid amorphous dispersions, and because document D5 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. In their view document D5 actually taught away from air-

jet milling, because it described a method to avoid post-crystallization milling (see D5, paragraph [0011].

These arguments are not convincing, because they fail to acknowledge on the one hand that document D8 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 D5 describes a special crystallization 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 D5 may be expected to allow for enhanced bioavailability. Moreover, in line with the common general knowledge, (see documents D119-D121) document D5 recognizes that such products with high purity, high stability and high surface area can also be obtained by high intensity milling of large crystals (see D5, paragraph [0004]).

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 10.2.3.3.4), 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 D5 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, for instance by air-jet milling, to enhance the dissolution of apixaban from an IR tablet.

4.3.7 According to the decision under appeal (see section 10.2.3.3.6) the evidence regarding the success of the product Eliquis(R) as reported in documents D97-D99 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 D8 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 D8 as closest prior art take account of the technical disclosure of document D8 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 1-6 (inventive step)

The additional definition of the conditions for the dissolution test in claim 1 of auxiliary request 1, 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 D8, 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 1 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 1 is also not considered to meet the requirement of inventive step.

In auxiliary requests 2-5 the amount of apixaban in the tablet is defined more restrictively than in auxiliary request 1. However, the amount of apixaban defined in auxiliary requests 2-5 still includes 5 mg as already described in document D8. Auxiliary requests 2-5 do thus not define any additional distinguishing feature with respect to the closest prior art and therefore do not meet the requirement of inventive step for the same reasons as set out for the auxiliary request 1.

Claim 1 of auxiliary request 6 more specifically defines the apixaban particles to have a D_{90} of less than 25 µm. The Board observes that document D5 already

describes the preparation of crystalline apixaban having a particle size of less than 20 µm and that in accordance with the common general knowledge as described in for instance document D120 air-jet milling is an attractive method to achieve particle sizes in the range of 1-30 µm. As the patent proprietors have not relied on any unexpected effect related to the particles having a D_{90} of less than 25 µm the Board therefore concludes that the subject-matter of claim 1 of auxiliary request 6 also lacks an inventive step.

7. Auxiliary request 7 (inventive step)

The additional feature in auxiliary request 7 with respect to auxiliary request 6, that the tablet is for use in the treatment of a thromboembolic disorder, corresponds with the known indication for apixaban already mentioned in document D8 in the section "Background of the invention" (see D8, 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 D8. This features does thus not relate to any effective technical contribution over the prior art.

The additional feature in auxiliary request 7 does therefore not overcome the objection of lack of inventive step against the subject-matter of claim 1 of auxiliary request 6. Accordingly, auxiliary request 7 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 1-6 do not meet the requirement of inventive step in view of document D8 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