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Datasheet for the decision of 2 December 2022

Case Number: T 0670/20 - 3.3.07

Application Number: 08720658.7

Publication Number: 2140867

IPC: A61K9/28, A61K31/444, A61K47/26, A61K47/32, A61K47/36, A61K47/38, A61P7/02, A61K9/20, A61P9/10

Language of the proceedings: EN

Title of invention:
PHARMACEUTICAL COMPOSITION

Patent Proprietor:
Daiichi Sankyo Company, Limited

Opponents:
Hexal AG
Generics [UK] Ltd

Headword:
Pharmaceutcial composition/SANKYO

Relevant legal provisions:
EPC Art. 123(2), 54, 56
RPBA 2020 Art. 13(1)

Keyword:
Amendments - allowable (yes)
Novelty - public prior use (no)
Inventive step - bonus effect (no)
Amendment to appeal case - justification by party (yes)

Decisions cited:
T 0007/07, T 0192/82

Catchword:

The clinical trials were carried out in accordance with the EMEA Guidelines for Good Clinical Practice. These guidelines explicitly require adherence to the prescribed protocol and assurance of drug accountability. This set-up of the trials implies that the patients who decided to participate in the trials agreed, following their informed consent, to use the provided medication according to instruction or to return the unused medication. Accordingly, the participating patients who were provided with the tablets under investigation entered into a special relationship with the investigators of the trials and were with regard to the provided tablets not members of the public that could freely dispose over these tablets. (see section 4.3)

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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 0670/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 2 December 2022

Appellant: (Opponent 1)	Hexal AG Industriestrasse 25 83607 Holzkirchen (DE)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Appellant: (Opponent 2)	Generics [UK] Ltd Station Close Potters Bar Hertfordshire EN6 1TL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Daiichi Sankyo Company, Limited 3-5-1, Nihonbashi Honcho Chuo-ku Tokyo 103-8426 (JP)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 24 January 2020 concerning maintenance of the European Patent No. 2140867 in amended form.**

Composition of the Board:

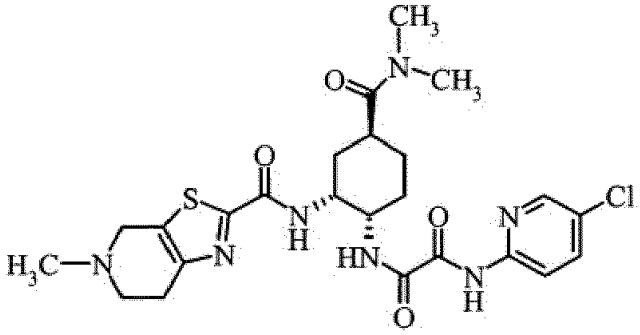
Chairman	A. Usuelli
Members:	M. Steendijk
	L. Basterreix

Summary of Facts and Submissions

I. European patent 2 140 867 ("the patent") was granted on the basis of ten claims.

Claim 1 as granted relates to:

"A pharmaceutical composition,
wherein the composition is a coated tablet,
wherein the coated tablet is a tablet coated with at least one coating agent selected from the group consisting of hypromellose, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, and polyvinyl alcohol,
wherein the tablet comprises:
(A) N^1-(5-chloropyridin-2-yl)-N^2-((1S,2R,4S)-4-[(dimethylamino)carbonyl]-2-{[(5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)carbonyl]amino}cyclohexyl)ethanediamide, represented by formula (1):



(1)

, a pharmacologically acceptable salt thereof, or a hydrate of any of these;
(B) a sugar alcohol; and
(C) a water-swelling additive."

The compound of formula (1) is herein further referred to by its present common name "edoxaban".

II. Two oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step and that the patent comprised subject-matter extending beyond the content of the application as filed. The opponents 01 and 02 filed appeals against the interlocutory decision of the opposition division that the patent as amended in accordance with the main request filed on 12 August 2019 met the requirements of the EPC.

Claim 1 of the main request differed from claim 1 as granted in that it defined component C of the compositions as follows:

"(C) pregelatinised starch or crystalline cellulose as a water-swelling additive."

The opposition division cited *inter alia* the following documents:

D3: US 2005/0119486 A1
D7: Remington: The Science and Practice of Pharmacy, 20th Ed., 2000, p.860, 863, 896-897
D11: Indian J. Pharm. Sci., 2007, 633-635
D19: www.clinicaltrial.gov; Identifier: NCT00107900 "Study of the Efficacy and Safety of DU-176b in Preventing Blood Clots in Patients Undergoing Total Hip Replacement" Available from: https:// clinicaltrials.gov/ct2/show/NCT00107900
D20: www.clinicaltrial.gov; Identifier: NCT00398216 "A Study of DU-176b in Preventing Blood Clots After Hip Replacement Surgery" Available from: https :// clinicaltrials.gov/ct2/show/NCT00398216

D21: Assessment report published by the European Medicines Agency for Lixiana (Edoxaban) EMA/321083/2015
D22: The Handbook of Pharmaceutical Excipients, 5th Ed, 2005, p.266-267, 278-282, 336-339, 449-453, 592-593, 725-731 and 824-827
D23: Aulton, "Pharmaceutics: The science of dosage form design", 2001, p. 4, 249, 296, 302, 341, 368 and 442
D24: US 5,506,248
D26: "Confirmatory Experiments", 22 November 2013
D27: EP 2548556 A1
D29: Redacted protocol of DU176b-PRT007
D30: Redacted protocol of DU176b-PRT011
D31: Confidentiality agreement Investigator PRT007
D32: Confidentiality agreement investigator PRT011
D33: EMEA Guideline for Good Clinical Practice - ICH Topic E 6 (R1)
D39: Lieberman, "Pharmaceutical Dosage Forms: Tablets, volume 1", 1989, p. 99, 100, and 210

The opposition division arrived at the following conclusions:

(a) Claim 1 of the main request was adequately based on the application as originally filed, which indicated that the defined combination of a sugar alcohol and a water-swelling additive, in particular pre-gelatinized starch or crystalline cellulose, as well as the defined coating agents were preferred.

(b) The priority was not valid, because the priority document did not specifically disclose the composition comprising edoxaban as defined in claim 1 of the main request. Consequently, document D11, which was published after the priority date and

before the filing date of the patent, represented prior art.

(c) The subject-matter of claim 1 of the main request was not anticipated by the alleged public prior use during the clinical trials described in documents D19 and D20.

In view of the evidence in documents D29-D33 the investigators and the test subjects could not be considered as members of the public. The circumstances differed from the case of T 7/07.

(d) Document D3 represented the closest prior art. This document described pharmaceutical preparations of edoxaban in general terms, but failed to describe an edoxaban tablet with the specific coating agents, a sugar alcohol and the water swelling additive as defined in claim 1 of the main request.

The experimental data presented in the patent and document D26 demonstrated improved dissolution of the pharmaceutical composition defined in claim 1 of the main request with respect to tablets comprising lactose and cornstarch, uncoated tablets and tablets provided with an enteric coating. The problem to be solved was formulated as the provision of a tablet with improved dissolution properties.

The subject-matter of claim 1 as granted was not obvious to the skilled person as none of the cited documents from the prior art suggested the particular combination of features in order to solve the stated problem.

III. With the reply to the appeals the respondent maintained the main request on which the decision under appeal was based.

IV. With its letter of 5 February 2021 appellant-opponent 1 filed the following document:

D40: Webpage from Colorcon, Starch 1500®, Partially pregelatinized maize starch (https://www.colorcon.com/products-formulation/all-products/excipients/tablets/starch-1500), downloaded 11 January 2021.

V. In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that document D40 was to be admitted, that the main request complies with Article 123(2) EPC and that the claimed subject-matter was new and involved an inventive step over the prior art.

VI. Oral proceedings were held on 2 December 2022.

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

- Amendments

  Claim 1 of the main request involved with respect to the content of the application as originally filed multiple selections involving i) the presence of both a sugar alcohol and a water-swelling additive, ii) the definition of the particular excipients and iii) the definition of the composition as a coated tablet.

- Priority

The opposition division correctly found that the priority document did not disclose the composition defined in claim 1 of the main request.

- Novelty

Claim 1 of the main request lacked novelty, because during the clinical trials described in documents D19 and D20 a composition within the scope of this claim had been made available to the participating patients as members of the public. Similar considerations as set out in T 7/07 applied.

- Inventive step

The difference of the composition of claim 1 of the main request with the disclosure in document D3 concerned the definition of the excipients of the composition comprising edoxaban. The experimental results on file merely demonstrated the suitability of the defined excipients to provide for an immediate release formulation. In view of document D23 it was further not credible that the defined coating contributed to the rapid dissolution of the tablets over the whole scope of the claims. The objective problem was therefore to provide a formulation suitable for immediate release of edoxaban. Sugar alcohols such as mannitol and water-swelling agents such as pre-gelatinised starch or crystalline cellulose represented conventional tablet excipients and had been recommended for achieving rapid dissolution. Moreover, it was an entirely conventional procedure to provide tablets with a coating. Any contribution to the rapid dissolution of the tablets from the coating represented a mere bonus effect.

In as far as pre-gelatinized starch could not be identified as the form of starch comprised in the composition made available during the clinical trials described in documents D19 and D20, it would be obvious to the skilled person to use pre-gelatinized starch in view of the known beneficial effect from this excipient on the dissolution properties of tablets.

VIII. The arguments of the respondent relevant to the present decision are summarized as follows:

- Amendments

The application as filed disclosed a coated tablet with the ingredients as defined in claim 1 of the main request, including the combination of the sugar alcohol and the water swelling additive, as most preferred embodiment.

- Priority

The priority document described edoxaban as the preferred active agent and disclosed the remaining features of claim 1 of the main request in claims 5, 9, 10 and 19 as a preferred embodiment.

- Novelty

The clinical trials of documents D19 and D20 did not render the claimed compositions available to the public. As was evident from documents D29-D33 the participating patients were not free to dispose over the provided medication. The considerations in T 7/07 did therefore not apply.

- Inventive step

Document D3 was the only cited document relating to edoxaban. This document failed to describe any specific formulation comprising edoxaban for comparison with the claimed composition and thereby demonstrated that the claimed subject-matter was from the outset based on an inventive step.

The claimed subject-matter differed from the teaching in document D3 in the choice of the tablet form, the coating of the tablet and the coating agents, and the presence of the sugar alcohol together with the pre-gelatinized starch or crystalline cellulose.

The patent presented the objective technical problem as the provision of an edoxaban formulation with excellent dissolution properties. The experimental results on file demonstrated that the formulation as a coated tablet and the choice of the excipients as defined in the claims of the main request interactively contributed to the excellent dissolution properties of the tablets. In view of the prior art the claimed composition was not obvious as solution to the objective problem, in particular having regard to document D23, which indicated that coatings do not enhance the dissolution rates of tablets.

The composition used in the clinical trials described in documents D19 and D20 was not available to the public and did therefore not represent a suitable starting point in the prior art.

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

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

Reasons for the Decision

1. Admittance of document D40

Appellant-opponent 01 filed document D40 with its letter of 5 February 2021 to support the argument that Starch 1500 as mentioned in documents D22 and D39 is a form of pre-gelatinised starch as defined in claim 1 of the main request. This had been contested for the first time in the respondent's reply to the appeal. The Board therefore considers the admittance of document D40 justified under Article 13(1) RPBA.

Main request

2. Amendments

The following explanations refer to the application published as EP 2 140 867 A1 for the content of the application as originally filed.

The application as filed discloses the coating agent as preferably selected from a cellulose derivative such as hypromellose, methyl cellulose, ethyl cellulose and hydroxypropyl cellulose, and a polyvinyl compound such

as polyvinyl alcohol (see paragraphs [0020] and [0021]).

The application as filed further defines in claims 1, 4, 11, 12 and 22 a coated tablet and highlights in paragraphs [0025], [0030] and [0031] as well as the examples the combined presence of the sugar alcohol and the water swelling additive, in particular pre-gelatinized starch and crystalline cellulose, as preferred.

The Board therefore agrees with the decision under appeal (see page 10, section 2.4) that claim 1 of the main request does not comprise subject-matter extending beyond the content of the application as originally filed and that the main request thus complies with Article 123(2) EPC.

3. Priority

The priority document discloses the formulation of a compound of a defined general formula in a pharmaceutical composition together with a coating agent (see claim 1). The coating agent may be selected from a variety of species (see claim 5), including amongst others the coatings agents as defined in claim 1 of the main request. The described pharmaceutical composition may further contain a diluent, including amongst others mannitol, and pre-gelatinized starch as water swelling additive (see claims 9-10). The described pharmaceutical composition may be formulated as a tablet, granule or powder (see claim 19).

The priority document further describes edoxaban p-toluene sulfonate ("Compound 1a") in a list of examples of compounds of the defined general formula which are

equally qualified as preferred (see translation D2, page 29, paragraph [0065] and page 30, third compound of paragraph [0066]). The examples of the priority document relate to specific tablet formulations comprising this particular salt of edoxaban.

The priority document does thereby not specifically disclose a coated tablet with the particular combination of excipients as defined in claim 1 of the main request, let alone such a coated tablet specifically comprising edoxaban or its salts or hydrates.

Accordingly, the Board agrees with the decision under appeal that the priority document does not disclose the composition as defined in claim 1 of the main request and that document D11 is therefore part of the prior art.

4. Novelty

4.1 Documents D19 and D20 relate to phase IIa and phase IIb clinical trials in which patients received treatment for the prevention of venous thromboembolism following hip surgery involving administration of edoxaban for a period of up to ten days. Document D21 (see page 15, line 8) indicates that the edoxaban formulation under investigation during the clinical studies described in documents D19 and D20 was the same as the formulation used for marketing. This formulation consisted of a tablet core of edoxaban tosilate with mannitol, pregelatinised starch, crospovidone, hydroxypropylcellulose and magnesium stearate and a film coating from hypromellose, macrogol 8000, titanium oxide, talc, carnauba wax, iron oxide yellow and iron oxide red (see D21, page 11, section 2.2.1).

It was not in dispute that the clinical trials described in documents D19 and D20 had started before the priority date claimed for the patent and that the trials concerned edoxaban tablets which were covered by the definition of claim 1 of the main request.

4.2 The appellants did not contest that the investigators involved in the trials were, as suggested in documents D31 and D32, bound to confidentiality and could therefore not be considered as part of the public that had access to information regarding the internal structure of the used tablets.

The appellants did further not contend that the participating patients had actually been directly informed of the internal structure of the tablets under investigation.

Instead, the appellants relied with reference to document D29 (section 4.5.4) and document D30 (see section 5.1) on the provision of the tablets under investigation during the trials of documents D19 and D20 to the participating patients who were discharged from hospital before the end of the treatment period. This provision of the tablets to the patients discharged from hospital before the end of the treatment was not contested by the respondent.

The assessment of the ground of lack of novelty in view of the trials described in documents D19 and D20 therefore crucially depends on whether the participating patients who received the tablets are to be considered as members of the public who were free to dispose over the provided tablets and thus

theoretically in a position to investigate the internal structure of the tablets.

4.3 Documents D29 and D30 represent the clinical trial protocols for the studies disclosed respectively in documents D19 and D20. According to document D29 (see sections 4.5.4 and 4.7.2.3) and document D30 (see sections 3.10 and sections 5.1 and 5.5) the investigators in the trials of documents D19 and D20 were instructed to ensure drug accountability and to monitor treatment compliance by taking account of the unused medication returned by the patients discharged from hospital.

As further pointed out by the respondent and not contested by the appellants the clinical trials of documents D19 and D20 were carried out in accordance with the EMEA Guidelines for Good Clinical Practice (document D33). These guidelines explicitly require adherence to the prescribed protocol (see D33, sections 2.6 and 2.12) and assurance of drug accountability (see D33, sections 4.6.1, 4.6.5 and 4.6.6).

This set-up of the trials of documents D19 and D20 implies that the patients who decided to participate in the trials agreed, following their informed consent, to use the provided medication according to instruction or to return the unused medication.

Accordingly, the participating patients who were provided with the tablets under investigation entered into a special relationship with the investigators of the trials and were with regard to the provided tablets not members of the public that could freely dispose over these tablets.

4.4 The appellants argued that the patients participating in the trials were not bound by any confidentiality agreement, which was evident from the statements in documents D19 and D20 that patients were encouraged to discuss their participation with their doctor, relatives and friends (see D19/D20, under "Eligibility Criteria"). According to the appellants it would actually be unethical to bind a patient to a duty of confidence that prevented them from discussing the trial with their doctor, family members or friends.

The Board acknowledges that the statements in documents D19 and D20 encouraging patients to discuss their participation in the trials indicates that the patients were not under a duty of confidence with respect to their participation to the trials and the information regarding the trial provided to them in that context. In fact, a duty of confidence regarding such information could be considered to constrain the patients in their ability to freely decide on participating in the trials on the basis of their informed consent, which would seem contrary to the above mentioned guidelines (see document D33, section 4.8).

However, the Board finds no reason why the absence of the patients' duty of confidence with respect to the information relevant to their participation in the trials should affect the obligations of the participating patients regarding the use and return of the tablets provided to them, which resulted from their decision to participate in the trials as explained in section 4.3 above.

4.5 The appellants further argued that the patients may have been requested to return unused tablets, but that

in the absence of any legal sanction no parallel to a confidentiality agreement could be assumed on such basis, especially as full compliance by all patients would not be likely.

The Board notes, however, that the patients' agreement to use the provided medication according to instruction or to return the unused medication obliges the patients irrespectively of any sanction on non-compliance and therefore disqualifies the patients as members of the public with respect to the medication provided to them.

The possibility of non-compliance to the instructed use and return of the tablets by the participating patients does not affect the essence of this agreement. Moreover, the appellants' estimation regarding the likelihood of full compliance remained speculative and therefore without consequence.

4.6 In T 7/07 the competent board concluded on the basis of the available information that apparently the sponsor of the trial had effectively lost control over the drugs after these had been handed out to the participants of the trial as members of the public who were not bound to secrecy (see section 3.3, pages 17-18, bridging paragraph, and section 3.6, page 22, lines lines 5-11). In view of the explanations in sections 4.3-4.5 above the Board considers that in the present case the tablets were not provided to the participants of the trial as members of the public, which distinguishes the circumstances of the trials of documents D19 and D20 from the circumstances of the trial considered in T 7/07.

4.7 Accordingly, the Board agrees with the finding in the decision under appeal (see page 22, lines 1-3) that the

public did not gain access to the claimed tablets during the trials reported in documents D19 and D20 and that the main request therefore complies with the requirement of novelty.

5. Inventive step

5.1 Closest prior art

5.1.1 Document D3 discloses edoxaban hydrochloride (see D3, page 203, example 192) in a list of examples of orally administrable anti-thrombotic agents (see D3, page 1, paragraph [0006]) which may be formulated with suitable additives, for instance in the form of a tablet (see D3, page 41, paragraphs [0370] to [0374]).

The teaching in document D3 differs from the subject-matter of claim 1 of the main request in that it only refers to formulations for the mentioned anti-thrombotic agents in general terms and does not reveal the constitution of an actual tablet comprising edoxaban.

In view of the disclosure of edoxaban hydrochloride as an example of an orally administrable anti-thrombotic agent the Board agrees with the finding in the decision under appeal (see page 22, section 3.5) that document D3 represents a suitable starting point in the prior art and thus dismisses the respondents argument that the teaching of document D3 is so remote from the claimed subject-matter that an inventive step should be recognized from the outset without the need for a further analysis in accordance with the problem-solution approach.

5.1.2 As explained in section 4.7 above the tablets used in the trials of documents D19 and D20 were not available to to public and therefore cannot serve as starting point in the prior art.

5.2 Formulation of the problem to be solved

5.2.1 The patent defines the object of the claimed invention as the provision of a pharmaceutical composition comprising edoxaban as active ingredient which exhibits excellent dissolution properties (see paragraph [0006]).

The experimental results from Example 1 of the patent (see paragraph [0066]) demonstrate that in a solution buffered at pH 4.0 tablets comprising a combination of mannitol with pre-gelatinized starch (D) or crystalline cellulose (E) show superior dissolution in comparison with the tablets (A), (B) and (C)in which lactose and/ or cornstarch is used instead (see Figure 1).

The experimental results from Example 3 of the patent (see paragraph [0073]) demonstrate that in a 0.1 N HCl solution as well as in water tablets comprising a combination of mannitol with pre-gelatinized starch (M) or crystalline cellulose (N) show superior dissolution over the tablets (J), (K) and (L)comprising lactose and/or cornstarch (see Figures 3 and 4), whereas in a solution buffered at pH 6.8 the tablet comprising lactose and pre-gelatinized starch (L) shows the faster dissolution (see Figure 5).

Example 4 of the patent relates to tablets comprising mannitol and pre-gelatinized starch (see paragraph [0077]). The experimental results from this example demonstrate that:

- in a solution buffered at pH 6.8 tablets with a 10 mg or 3 mg hypromellose based coating show superior dissolution over the non-coated tablet (see Figure 6),

- in a solution buffered at pH 6.8 tablets with a 10 mg coating based on hypromellose, ethylcellulose or polyvinyl alcohol show superior dissolution over the tablets which are not coated or coated with a methacrylic acid copolymer (see Figure 7),

- tablets with a 10 mg hypromellose based coating are rapidly completely dissolved in buffered solutions with pH 4.0 or pH 4.5 (see Figure 8).

5.2.2 The appellants contested the relevance of the experimental results reported in the patent as follows:

(a) Document D22 (see page 30, section 7) and document D39 (see page 100, Figure 6) indicated that cornstarch was known to have inferior qualities as excipient compared to pre-gelatinised starch. Moreover, document D7 (see page 860, under "Diluents") listed lactose and mannitol as equally preferable diluents.

Compositions comprising lactose or cornstarch should therefore not by default be considered as representative for compositions of the closest prior art. The comparison with tablets comprising these excipients in Figures 1 and 3-5 was therefore not suitable to demonstrate any unexpected effect for the tablets defined in claim 1 of the main request.

(b) The results for the dissolution of the tablets at pH 4.0 and 4.5 reported in Figure 8 of the patent did not present any comparison between coated and non-coated tablets. The results reported in Figures 6-7 only concerned the dissolution of tablets at pH 6.8, which would not be of any practical relevance. The apparently enhanced dissolution of the coated tablets over the uncoated tablets reported in Figures 6-7 was furthermore not consistent with the results from Figure 5, which showed for the uncoated tablet (M) the same rate of dissolution at pH 6.8 as reported in Figures 6 and 7 for coated tablets having the same core-components. Moreover, document D27 indicated in Figure A-1 a lower dissolution rate for coated tablets compared to the uncoated tablet in Figure 6 of the patent. The results in Figures 6 and 7 were also not in line with the expectations based on document D23, which indicated (see page 249, bridging section left and right column) that thin coatings of water-soluble polymers such as hydroxypropyl methyl cellulose have no effect on the tablet dissolution and that coatings from hydrophobic material, such as ethylcellulose, actually act as a barrier which reduces the rate of drug release from the tablet.

The results reported in Figures 6-8 would therefore not convincingly show any improved dissolution from the coated tablets with respect to the non-coated tablets.

(c) Even if the results reported in Figures 6-8 were considered to show any unexpectedly improved dissolution from the tested coated tablets over the non-coated tablets, such effect remained unexplained and could therefore not be plausibly

extrapolated to tablets comprising alternative forms of edoxaban, alternative sugar alcohols, crystalline cellulose instead of pre-gelatinized starch, tablets without a disintegrant or tablets prepared by different tableting methods.

5.2.3 As observed in section 5.1.1 above document D3 does not describe any particular tablet composition. In view of this lack of information in document D3 any outstanding qualities of the tablets as claimed, such as their excellent dissolution properties, may in the Board's view well be demonstrated by a comparison with edoxaban tablets having a conventional structure and prepared with conventional excipients. Document D7 (see page 860, left column), document D22 (see pages 725-726) and document D39 (see pages 99 and 210) confirm that lactose and corn-starch as well as mannitol, pre-gelatinized starch (such as Starch 1500, see D40) and crystalline cellulose represented widely used, conventional tablet excipients. Moreover, as indicated by document D23 (see page 249, bridging paragraph between left and right column) the dissolution of uncoated tablets is typically not enhanced by a coating of the type as defined for the claimed tablets. The Board therefore considers the comparison of tablets comprising mannitol and pre-gelatinized starch or crystalline cellulose with tablets comprising lactose or cornstarch together with the comparison between the non-coated tablets and the coated tablets with the same tablet-core as reported in the examples of the patent suitable to demonstrate that the coated structure and the choice of the excipients contribute to the excellent dissolution properties of the tablets as defined in accordance with the main request.

The results reported in Figures 6-7 of the patent allow for the direct comparison of the dissolution rates of the coated and uncoated tablets prepared under the conditions of Example 4. The comparison of these tablets, which only differ in the applied coating, justifies the conclusion in the patent (see paragraphs [0078] to [0080]) that the coating of the tablets contributes to the excellent dissolution of the tablets in a buffered solution at pH 6.8. The uncoated tablet formulation (M) in Example 3 of the patent was prepared by applying a different force for the tablet compression than the force applied for the formulations of Example 4 of the patent (7.5 instead of 10 kN). The results in Figure A-1 of document D27 concern coated tablets prepared under special conditions involving high moisturization (see D27, page 13, Table 4). The dissolution of the uncoated tablet formulation (M) of Example 3 reported in the patent and of the coated tablet reported in document D27 may well have been affected by differences in the preparation of the tablet cores and do therefore not invalidate the conclusion regarding the effect of the coating on the dissolution based on the results of Example 4.

The rapid and complete dissolution of the hypromellose coated tablets at pH 4.0 and 4.5 reported in Figure 8 of the patent further confirm the excellent dissolution of the coated tablets of Example 4 of the patent as demonstrated in Figures 6-7 at pH 6.8. Moreover, as pointed out by the respondent during the oral proceedings and not contested by the appellants, the dissolution rate of tablets at pH 6.8 is for instance of practical relevance in patients having close to neutral pH levels in the stomach due to treatment with proton pump inhibitors. The excellent dissolution of the coated tablets of Example 4 demonstrated in the

patent may therefore not be dismissed as lacking practical relevance.

The results in Figures 1, 3-5 and 6-8 of the patent demonstrate that the choice of the components and coated structure of tablets as defined in claim 1 of the main request contribute to the rapid dissolution rates of the tablets. Enhanced dissolution was even observed with the use of ethylcellulose as coating agent (see Figure 7), which according to document D23 was actually expected to impede tablet dissolution. In the absence of evidence to the contrary the credibility of the effect of the choice of the components and the structure of the patent is not effectively challenged, merely because this effect could not be expected or explained in view of document D23.

5.2.4 Accordingly, the Board considers that in line with paragraph [0006] of the patent the problem to be solved may be formulated as the provision of a solid pharmaceutical composition comprising edoxaban as active ingredient which allows for excellent dissolution properties.

5.3 Assessment of the solution

5.3.1 As argued by the appellants sugar alcohols such as mannitol and the swelling additives crystalline cellulose and pre-gelatinised starch were well known excipients for use in tablet formulations (see for instance documents D7, D22 and D39 as mentioned in section 5.2.3 above). Moreover, documents D11 (see page 634, left hand column) and D24 (see for instance Example 1) describe the combination of these excipients in fast dissolving tablet formulations. As evidenced by document D23 it indeed was also well known to provide

tablets with a coating for various practical purposes (see D23, page 249).

However, the cited prior art provided the skilled person with no reasonable expectation that the use of a combination of a sugar alcohol with pre-gelatinized starch or crystalline cellulose as a water-swelling additive allowed the dissolution of tablets comprising edoxaban to be still further enhanced by coating the tablet with a coating agent as defined in claim 1 of the main request. On the contrary, as indicated in document D23 tablet coatings were expected to have a detrimental effect on the dissolution properties or, in case of thin water-soluble polymers, to have at best no particular effect on dissolution rate of the tablets (see D23, page 249, paragraph bridging left and right column).

The skilled person would therefore not have arrived as a matter of obviousness at a tablet as defined in the main request in order to provide a pharmaceutical composition comprising edoxaban which allows for excellent dissolution properties.

5.3.2 The appellants argued that the claimed tablets should be denied an inventive step irrespective of any unexpected dissolution characteristics, because the defined coated structure and the defined excipients were entirely conventional for immediate release tablet formulations, in view of which any unexpected dissolution characteristics would represent a mere bonus effect.

The Board observes that technical effects associated with the distinguishing features of a claimed invention have been disregarded as a mere "bonus effect" in the

jurisprudence of the Boards of Appeal in special cases in which the skilled person was actually bound to arrive at the claimed subject-matter, for instance because alternatives were absent for solving a realistic technical problem and the skilled person was thus in a so-called "one-way street" situation (see T 192/82, OJ EPO 1984, 415; see also Case Law of the Boards of Appeal of EPO, 10th Edition 2022, I.D.10.8).

In view of the availability of alternative excipients for preparing tablets as for instance discussed in document D7 (see page 860, left column, under "Diluents") it is not evident that starting from document D3 the skilled person was bound to arrive at the coated tablets as defined in accordance with the main request. The Board finds therefore no convincing reason to dismiss the excellent dissolution properties of the claimed tablets as a mere bonus effect.

5.4 Accordingly, the Board agrees with the decision under appeal that the subject-matter of claim 1 of the main request also involves an inventive step.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated