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Datasheet for the decision of 8 January 2018

Case Number: T 1460/13 - 3.3.01

Application Number: 07850165.7

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Language of the proceedings: EN

Title of invention:
METHOD FOR PRODUCING SOLID PREPARATION

Applicant:
Daiichi Sankyo Company, Limited
Ube Industries, Ltd.

Relevant legal provisions:
EPC Art. 56
RPBA Art. 12(4)

Keyword:
Inventive step - (no)
Late-filed request - admission (no); request withdrawn in first instance proceedings

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Case Number: T 1460/13 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 8 January 2018

Appellant: (Applicant 1)	Daiichi Sankyo Company, Limited 3-5-1, Nihonbashi Honcho Chuo-ku Tokyo 103-8426 (JP)
Appellant: (Applicant 2)	Ube Industries, Ltd. 1978-96, Ooaza Kogushi Ube-shi Yamaguchi 755-8633 (JP)
Representative:	Fairbairn, Angus Chisholm Marks & Clerk LLP 90 Long Acre London WC2E 9RA (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 11 December 2012 refusing European patent application No. 07850165.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Lindner
Members:	R. Hauss
	L. Bühler

Summary of Facts and Submissions

I. The present appeal lies from the decision of the examining division, announced on 17 October 2012 and posted on 11 December 2012, refusing European patent application No. 07 850 165.7.

II. The documents cited in the course of the examination and appeal proceedings include the following:

D11: WO 2004/098713 A2

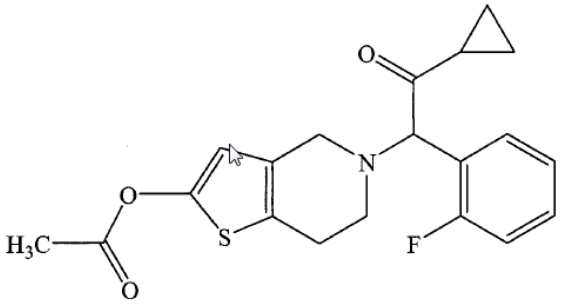
D18: Guidance for Industry, SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms - Manufacturing Equipment Addendum, CMC 9 Revision 1 (January 1999)

III. In the course of the examination proceedings, the applicants presented an amended main request and three auxiliary requests, all filed with letter dated 16 March 2012. During oral proceedings before the examining division on 17 October 2012, the applicants withdrew the second and third auxiliary requests and submitted another set of claims as their new second auxiliary request.

IV. The decision under appeal is thus based on a main request and two auxiliary requests.

Independent claim 1 of the main request reads as follows:

"1. A method for producing a solid preparation containing a compound represented by the following general formula (I):



(I)

or a pharmacologically acceptable salt thereof, comprising a step wherein a composition containing the compound represented by the aforementioned general formula (I) or a pharmacologically acceptable salt thereof is mixed by using a convection mixer equipped with a stirring blade and rotating the stirring blade such that the circumferential velocity at the end of the stirring blade is 5.0 m/s to 20 m/s."

The compound according to formula (I) is also known as "prasugrel".

The wording of independent claim 1 of the first auxiliary request is identical to that of claim 1 of the main request, except that the range defined for the circumferential velocity at the end of the stirring blade is replaced by the value *"14.1 m/s"*.

V. In the decision under appeal, the examining division found that the subject-matter of claim 1 of the main request did not involve an inventive step within the meaning of Article 56 EPC:

Document D11 disclosed the manufacture of a solid preparation containing prasugrel involving a mixing step. The method for producing the preparation as defined in claim 1 differed from the disclosure of D11 in that the type and speed of the mixer were specified. It had not been rendered credible that the alleged

technical effect, viz. improved dissolvability of the solid preparation thus produced, was obtained over the entire scope claimed. The comparative test described in the application did not go beyond comparing two samples processed with two different mixers under very specific conditions. Since claim 1 covered many possible options with regard to the mixer and mixing conditions, and other variables (in terms of properties of the compositions) were known to affect the dissolution properties of the final product, the result of the comparative test could not be extrapolated to predict the outcome for different compositions to be mixed, or for different configurations of the mixing apparatus. Starting from the disclosure of document D11, the technical problem to be solved was to define a mixing method. Convection mixing was a standard method. In the absence of evidence of an unexpected technical effect, the selection of the correct impeller speed was a matter of routine not involving inventive skill.

For the same reasons, claim 1 of the first auxiliary request did not involve an inventive step.

The amendments in the first and second auxiliary requests introduced subject-matter extending beyond the content of the application as filed, contrary to Article 123(2) EPC.

VI. The applicants (appellants) filed notice of appeal against that decision.

VII. With the statement setting out the grounds of appeal, the appellants submitted four sets of claims as their main request and first to third auxiliary requests, all identical to the requests filed in the first-instance proceedings with letter of 16 March 2012.

The main request and first auxiliary request are thus identical to the corresponding requests which were examined in the decision under appeal (see point IV above).

The second and third auxiliary requests are identical to the requests which were withdrawn during oral proceedings on 17 October 2012 (see point III above and the minutes of the oral proceedings before the examining division: page 1, paragraph 1, and page 3, lines 1 and 2). The wording of these requests is identical to that of the present main request and first auxiliary request, respectively, with the sole difference that in claim 1 of each request, the term *"convection mixer"* is replaced by *"Henschel Mixer FM-20B"*.

VIII. In a communication issued in preparation for oral proceedings pursuant to Article 15(1) RPBA, the board gave a negative opinion on inventive step.

It also mentioned that it was likely that the second and third auxiliary requests would not be admitted into the proceedings, pursuant to Article 12(4) RPBA.

IX. Oral proceedings took place on 8 January 2018.

X. The appellants' arguments may be summarised as follows:

Inventive step - main request

Document D11 was a valid starting point for the assessment of inventive step. Starting from D11, the technical problem to be solved consisted in the provision of a method for producing a solid preparation of prasugrel which could achieve improved dissolution. According to the invention as defined in claim 1 of the main request, that problem was solved by applying

mechanical stress to the composition, more specifically by using a convection mixer equipped with a stirring blade and rotating the stirring blade such that the circumferential velocity at the end of the stirring blade was 5.0 m/s to 20 m/s. Neither D11 nor the other prior-art documents on file suggested taking those actions to achieve improved dissolution.

Contrary to the examining division's assessment given in the decision under appeal, the comparative test and resulting experimental data disclosed on pages 17 to 19 of the application rendered it credible that the technical problem relating to improved dissolution was solved over the entire scope claimed, for the following reasons:

(a) The comparison as reported in the application was appropriate, since two identical compositions containing prasugrel had been processed, the only difference being the mixing conditions applied. Thus there could be no doubt that the improvement in dissolution obtained with the sample representing the invention vs the comparative sample (as shown in table I on page 19) was due to the technical features distinguishing the claimed method from the disclosure of document D11. In that context, the mixing method chosen to process the comparative sample (by using a diffusion mixer) was adequately representative of the prior art D11, which did not require or suggest the use of a convection mixer.

(b) The invention was thus based on mechanical stress being applied to the compositions, regardless of the nature of the composition which was being processed. It was therefore credible that the same improvement in dissolution would be obtained when any composition containing prasugrel was processed

employing the method according to the invention, as compared to the method of the comparative example. While it was not disputed that certain properties of the compositions and their components might affect the dissolution behaviour of the final product, such effects would be cancelled out in a comparison in which only the mixing method, but not the composition, was varied.

(c) The circumferential velocity chosen according to example 1 for processing the sample representing the invention was 14.1 m/s, which was right in the middle of the range of 5.0 to 20 m/s defined in claim 1. It could plausibly be expected that the desired technical effect of improved dissolution would also be obtained at velocities similar to 14.1 m/s, i.e. those within the range claimed.

Inventive step - first auxiliary request

The first auxiliary request, which fixed the circumferential velocity at 14.1 m/s, had been drafted to counter the objection that the range of 5.0 m/s to 20 m/s defined in the main request was incommensurately broad. Apart from that, the same arguments applied as in the case of the main request.

Admission of the second and third auxiliary requests

The second and third auxiliary requests attempted to give a more precise definition of the convection mixer. In oral proceedings before the examining division, those same requests had been withdrawn and replaced by a different auxiliary request with a view to advancing the discussion, which at the time focused on the examining division's objection that the composition was insufficiently defined. It appeared equitable, however, that the board should permit the reinstatement of

former auxiliary requests 2 and 3, which had been submitted again with the grounds of appeal in case the board came to the conclusion that inventive step could only be acknowledged on the basis of a more precise definition of the mixer configuration.

XI. The appellants requested that the decision under appeal be set aside and that the case be remitted to the examining division for a patent to be granted on the basis of the main request or, alternatively, of one of the first to third auxiliary requests, all filed with the statement of grounds of appeal.

Reasons for the Decision

1. Main request - inventive step

Present application

1.1 The present application aims to provide a method for producing a solid preparation of prasugrel (or of a pharmacologically acceptable salt thereof) showing good dissolvability.

1.2 To that end, the application proposes a method which involves a mixing step employing a convection mixer equipped with a stirring blade which rotates at a specified velocity.

Starting point in the prior art

1.3 Formulations 2 to 4 described on page 17, line 7, to page 19, paragraph 2, of document D11 contain prasugrel (or a pharmaceutically acceptable salt, solvate, active metabolite, enantiomer or racemate or prodrug thereof) and excipients (microcrystalline cellulose, fumed

silica and stearic acid). As far as the process of preparation is concerned, it is mentioned that the components are blended and compressed to form a solid, which is then tableted or capsuled or admixed with an adhesion agent. Thus, document D11 discloses solid preparations containing prasugrel, and their production involving a mixing (or blending) step.

Technical problem and solution

1.4 Within the framework of the problem-and-solution approach employed as a rule by the boards for assessing inventive step, the objective technical problem is determined on the basis of a technical effect achieved by the claimed subject-matter when compared with the subject-matter which is the starting point in the prior art. For this purpose, an alleged technical effect can be taken into account only if it is achieved over the entire scope of the claim.

1.5 The method defined in claim 1 of the main request differs from the disclosure of D11 in that the general type and the speed of the mixer are specified, viz. the composition is to be mixed by using a convection mixer equipped with a stirring blade and rotating the stirring blade such that the circumferential velocity at the end of the stirring blade is 5.0 m/s to 20 m/s.

1.6 According to the appellants, the claimed method has the advantage that the solid preparations thus obtained show improved dissolution of the prasugrel component. In support of this alleged technical effect, the appellants relied on the comparative test which is described on pages 17 to 19 of the present application, arguing that the experimental data reported there rendered it credible that the alleged technical effect was obtained over the entire scope claimed.

1.7 The board does not reach the same conclusion, for the following reasons:

1.7.1 Scope of claim 1

In claim 1 of the main request, the composition which is to be processed to produce the desired solid preparation is not defined at all, except for the requirement that it must contain prasugrel or a pharmacologically acceptable salt thereof. Hence, any combination of excipients may be present, while the prasugrel component may vary in its chemical nature and its physical properties (such as crystallinity, morphology, particle size or surface properties).

Likewise, a broad variety of possible mixer configurations and mixing conditions is covered by the claim, which merely requires the use of a convection mixer equipped with a stirring blade which rotates at a circumferential velocity of 5.0 m/s to 20 m/s. In this, the term "convection mixer" indicates the general operating principle of the mixer; typical convection mixers use a fixed container with an internal rotating element (impeller) like a stirring blade, ribbon, paddle or plough (see also document D18). While claim 1 requires the presence of a stirring blade, it does not contain any restrictions with regard to the dimensions of the vessel or to the number, shape and configuration of the stirring blades.

1.7.2 Criteria for selecting a mixing method

The desired end result of a mixing process is typically the formation of a homogeneous mixture. The method of choice for achieving that aim may however be different for different substrates depending, for instance, on particle sizes, the flowability and electrostatic properties of powders, the cohesivity of the materials in question, their sensitivity to mechanical stress,

the ratios of the components and, importantly, on the desired properties of the composition after mixing, e.g. the requirements for the dissolution properties of the drug component in a solid pharmaceutical preparation. Thus it is well known in the field of pharmaceutical formulation that different mixer configurations and process conditions may be suitable, depending on the nature and properties of the composition to be mixed and on the properties required in the end product.

Accordingly, a great variety of mixer configurations and mixing parameters are commonly used for pharmaceutical formulation purposes (see, for instance, document D18, which distinguishes between diffusion blending, convection mixing and pneumatic mixing and lists a variety of mixer subclasses for each category).

1.7.3 Variables which may affect dissolvability

It was not contested by the appellants that various properties of the compositions and their components will affect the dissolution behaviour of the finished solid preparation. As pointed out by the examining division in the decision under appeal, drug particle agglomerate formation during the mixing process, which itself depends on a number of other variables, is a critical factor. Such variables may include particle size and shape, morphology, particle size ratios or drug/carrier ratio of the materials which are present for the mixing step.

As far as the mixing conditions and the interaction of the mixer with the composition are concerned, the mixer configuration and dimensions, the shape and rotating speed of the impeller, humidity, or batch size in relation to mixer volume may be mentioned as factors

which may have an impact on particle agglomeration and the properties of the final composition.

Any of the variables mentioned may have a positive or negative impact on dissolvability, with the total impact of all relevant variables depending on the individual case. As a consequence, it is not possible to extrapolate the result obtained for a specific set of those variables to a different set; in particular, it cannot be ruled out on that basis that a specific combination of mixing conditions may result in favourable dissolution properties for some compositions, but may be unsatisfactory in that respect for other compositions, which would require different mixing conditions to achieve good dissolution properties.

Thus the appellants' argument that the same kind of mechanical stress will produce the same result regardless of the nature of the composition must fail.

1.7.4 Consequences

It follows from points 1.7.2 and 1.7.3 that different combinations of operating principles, mixer configurations and mixing conditions may be suitable (or unsuitable) for different individual compositions, when the intention is to obtain mixtures of acceptable quality and/or to achieve good dissolution properties.

This is also true for the very broad range of compositions covered by the definition given in claim 1 (see point 1.7.1 above).

The comparative test described in the present application (see pages 17 and 18) establishes that a specific composition containing prasugrel hydrochloride, which was processed using one single method involving a mixing step as defined in claim 1

of the present main request, performed better in the dissolution test than an identical composition which was processed using one single different method not conforming to claim 1 with regard to the mixing step.

It is not possible to infer from the results of the comparative test that the specific mixing method used in example 1 of the application, involving a Henschel Mixer FM-20B, a circumferential velocity of the stirring blade of 14.1 m/s and a specific batch size, when used with any other composition containing prasugrel or a pharmacologically acceptable salt thereof, will always result in preparations with similar dissolution properties.

It is even less plausible that this should be the case not only for the specific method of example 1, but for all mixer configurations and mixing conditions covered by claim 1.

Conversely, the comparative test does not establish that a mixing method according to the state of the art, which may involve any suitable operating principle according to common general knowledge (including convection mixing using a stirring blade rotating at a speed outside the range of 5.0 to 20 m/s or using a different impeller), will result in a mixture with inferior performance in a dissolution test. The mixing method employed in the comparative example of the present application involved a diffusion mixer (V-type mixer) operated at specified conditions, but it is not even known if the operating conditions of the V-type mixer were optimised with regard to the dissolution properties of the finished product. The comparative example thus represents a single arbitrary choice within a very broad range of possible options. It is not possible to infer from the available information that any other mixing method which is not in conformity

with claim 1, when applied to any composition containing prasugrel or a pharmacologically suitable salt thereof, would inevitably give rise to similar dissolution properties which are furthermore less favourable than those achievable with any mixing method according to claim 1.

Hence, it has not been rendered credible that any method for producing a solid preparation of prasugrel or a pharmacologically acceptable salt thereof would yield a product with improved dissolution properties if a mixing step as defined in claim 1 were involved, as opposed to any conceivable production method using different mixing conditions, and independently of any other variables of said method which might affect the final product. The available experimental data relate to one specific case for comparison and do not permit such far-reaching extrapolation, since example 1 cannot be regarded as representative of the entire scope claimed, and the comparative example cannot be regarded as representative of the broad range of options not claimed. Nor have the appellants presented any supplementary data or theoretical considerations which could support such a conclusion.

1.8 As a consequence, the alleged technical effect of improved dissolution properties cannot be taken into account in formulating the objective technical problem. Starting from the disclosure of document D11, and without evidence of any other particular technical effect, the technical problem to be solved is thus the provision of a further method for producing a solid preparation containing prasugrel or a salt thereof.

1.9 The claimed solution as defined in claim 1 of the main request involves using a convection mixer and choosing a suitable stirring speed.

Obviousness of the solution

1.10 The person skilled in the art, reading the instruction in D11 that the components must be blended (i.e. mixed) and compressed, would contemplate using any known mixing method which might be suitable.

1.11 It cannot be derived from the information contained in document D11 that any mixer type or operating principle would, *a priori*, be considered unsuitable. It is, moreover, common general knowledge that a wide variety of mixer types using varying operating principles, including convection mixers, is employed in the pharmaceutical industry. The applicants did not contest that convection mixers (including models operating with a stirring blade) are well-known conventional mixers.

1.12 Hence the choice of a convection mixer with a rotating stirring blade is well within the scope and purview of document D11. So is the selection of an appropriate rotating speed (expressed in claim 1 as the circumferential velocity). There is no indication derivable from the prior art or common general knowledge which would keep the person skilled in the art from working in the range of 5.0 to 20 m/s.

1.13 The implementation of such measures lies within the scope of routine activities of the skilled formulator and therefore does not involve an inventive step.

1.14 As a consequence, the claimed subject-matter does not involve an inventive step within the meaning of Article 56 EPC.

2. First auxiliary request - inventive step

2.1 The amendment replacing the range with a specific value for the circumferential velocity does not change anything in the assessment of inventive step given above in section 1, viz. the finding that the comparative test in the patent application cannot render it credible that the claimed method for producing a solid composition containing prasugrel results in an advantage compared to any other method within the common general knowledge.

2.2 As a consequence, the subject-matter of claim 1 of the first auxiliary request does not involve an inventive step within the meaning of Article 56 EPC, for the same reasons as explained above in the context of claim 1 of the main request.

3. Admission of the second and third auxiliary requests into the proceedings

3.1 Article 12(4) RPBA provides the board with the discretionary power to hold inadmissible requests which could have been presented in the first-instance proceedings.

3.2 The present second and third auxiliary requests are identical to the former second and third auxiliary requests filed with letter of 16 March 2012. Those requests were withdrawn by the appellants, of their own volition, during oral proceedings before the examining division (see points III and VII above).

3.3 The reinstatement of requests which were withdrawn in the first-instance proceedings is contrary to the main purpose of appeal proceedings, which are primarily concerned with reviewing the correctness of the

contested decision. Such reinstatement would therefore, as a rule, not be regarded as appropriate unless justified by specific circumstances.

3.4 While, in oral proceedings before the examining division, the appellants filed a different new auxiliary request in reaction to a specific objection which was being discussed, nothing obliged them to withdraw their then pending second and third auxiliary requests at the same time. Had they wished to pursue those requests, they could and should have maintained them in order to obtain an appealable decision on them from the examining division.

3.5 Since there is no specific reason why the appellants could not have maintained their corresponding requests in the first-instance proceedings, the board exercises its discretion pursuant to Article 12(4), first half-sentence, RPBA, by not admitting the present second and third auxiliary requests into the appeal proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

M. Schalow A. Lindner

Decision electronically authenticated