

Internal distribution code:

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

**Datasheet for the decision
of 18 September 2018**

Case Number: T 0662/15 - 3.3.07

Application Number: 08807939.7

Publication Number: 2349220

IPC: A61K9/20, A61K31/395

Language of the proceedings: EN

Title of invention:

USING OF ORGANIC SOLVENTS IN WET GRANULATION OF MOXIFLOXACIN

Patent Proprietor:

Abdi Ibrahim Ilac Sanayi ve Ticaret Anonim Sirketi

Opponent:

Generics [UK] Limited

Headword:

USING OF ORGANIC SOLVENTS IN WET GRANULATION OF MOXIFLOXACIN/
Abdi Ibrahim Ilac Sanayi ve Ticaret Anonim Sirketi

Relevant legal provisions:

RPBA Art. 12(4)
EPC Art. 56

Keyword:

Decisions cited:

Catchword:



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 0662/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 18 September 2018

Appellant: Abdi Ibrahim Ilac Sanayi ve Ticaret Anonim
(Patent Proprietor) Sirketi
Abdi Ibrahim Uretim Tesisleri
Patent Departmani
Sanayi Mahallesi
Tunc Caddesi No. 3
Esenyurt
Istanbul (TR)

Representative: Krauss, Jan
Boehmert & Boehmert
Anwaltspartnerschaft mbB
Pettenkoferstrasse 22
80336 München (DE)

Respondent: Generics [UK] Limited
(Opponent) (trading as Mylan)
Albany Gate
Darkes Lane
Potters Bar
Hertfordshire EN6 1AG (GB)

Representative: FRKelly
27 Clyde Road
Dublin D04 F838 (IE)

Decision under appeal: **Decision of the Opposition Division of the
European Patent Office posted on 28 January 2015
revoking European patent No. 2349220 pursuant to
Article 101(3)(b) EPC.**

Composition of the Board:

Chairman J. Riolo
Members: D. Boulois
 C. Schmidt

Summary of Facts and Submissions

- I. European patent No. 2 349 220 was granted on the basis of a set of 3 claims.

Independent claim 1 as granted read as follows:

"1. A wet granulation method of anhydrous moxifloxacin or its salts characterized in that wetting agent is selected from group of isopropyl alcohol, acetone, ethanol, dichloromethane or mixtures thereof."

- II. An opposition was filed under Article 100 (a) and (b) EPC on the grounds that its subject-matter lacked novelty and inventive step and was not sufficiently disclosed.
- III. The appeal lies from the decision of the opposition division to revoke the patent. The decision was based on the claims as granted.
- IV. The documents cited during the opposition proceedings included the following:
D1: US 2005/031683 A1
D2 US 2007/196466 A1
D3: US 7 230 006 B2
D4: Handbook of Pharmaceutical Excipients, 4th Ed., published 2003, Chapter Cellulose, Microcrystalline, page 108; Chapter Povidone, page 508; edited by Raymond C. Rowe et al.
- V. According to the decision under appeal, the subject-matter of claim 1 as granted was sufficiently disclosed and was novel over D1.

As regards inventive step, D3 was considered as the closest prior art and disclosed a crystalline form of anhydrous moxifloxacin hydrochloride, its preparation and discloses that direct compression, wet granulation process and molding can be used for making tablets comprising this crystalline form of anhydrous moxifloxacin hydrochloride (D3, column 12, lines 13-14). Soluble granules of anhydrous moxifloxacin hydrochloride were disclosed in example 5 of D3 (col. 15). Other processes for the preparation of formulations comprising the same API (anhydrous moxifloxacin) were disclosed in D3, ex. 6-7.

Starting from D3 as closest prior art, the problem was first seen as the provision of an improved wet granulation method for the preparation of a solid formulation of anhydrous moxifloxacin with no or few conversion to moxifloxacin monohydrate. The solution as proposed in claim 1 was characterized in that the wetting agent was selected from isopropyl alcohol, acetone, ethanol, dichloromethan or mixtures thereof.

In the present case, there was apparently no effect shown concerning a decrease of the conversion to moxifloxacin monohydrate over the wet granulation processes of D3. As a consequence, the problem was reformulated as the provision of an alternative wet granulation method for the preparation of a solid formulation of anhydrous moxifloxacin. No further unexpected effect could be derived from the selection of the four specific solvents defined in the claims. Such an arbitrary selection could not be the basis for recognizing an inventive step. The solution provided in claim 1 was seen as obvious.

VI. The patent proprietor (hereinafter appellant) filed an appeal against said decision.

VII. With the statement setting out the grounds of appeal dated 3 June 2015 the appellant filed an auxiliary request 1.

Independent claim 1 of auxiliary request 1 read as follows, difference(s) compared with claim 1 of the main shown in bold:

"1. A wet granulation method of anhydrous moxifloxacin or its salts characterized in that wetting agent is selected from group of isopropyl alcohol, acetone, ethanol, dichloromethane or mixtures thereof, **wherein the anhydrous moxifloxacin salt is hydrochloride.**"

VIII. In its response to the statement of grounds of appeal, the opponent (hereafter respondent) requested that auxiliary request 1 not be admitted into the proceedings.

IX. A communication from the Board was sent to the parties. In this it was considered in particular that auxiliary request 1 should be admitted into the proceedings and that the main request and auxiliary request 1 did not appear to be inventive over D3.

X. Oral proceedings took place on 17 July 2014 with the announced absences of the appellant and respondent.

XI. The arguments of the appellant may be summarised as follows:

Inventive step

The problem of the invention was to provide a wet granulation method for the preparation of a solid formulation of anhydrous moxifloxacin with no/few conversion to moxifloxacin monohydrate. It was desired that the anhydrous moxifloxacin hydrochloride should permanently have properties of its own form without converting its form after wet granulation and becoming dosage form (para. [0005]).

D3 related to a crystalline Form III of moxifloxacin monohydrochloride and processes for making the crystalline form. D3 generally discussed many possible differences in the properties of different polymorphic forms, but did not discuss problems with water in the formulation of the compound, let alone moxifloxacin. D3 disclosed that a preferred oral solid preparation is a tablet, and that a tablet may be prepared by direct compression, wet granulation, or molding, of the active ingredient(s) with a carrier and other excipients in a known manner.

D3 differed from the present invention in that no specific tableting method of anhydrous moxifloxacin with a wetting agent selected from the group of isopropyl alcohol, acetone, ethanol, dichloromethane or mixtures thereof was disclosed.

The object of the present invention in view of D3 thus was seen as an improved wet granulation method for preparing anhydrous moxifloxacin tablets by avoiding water.

The solution was found in claim 1 of the patent in suit, where specific non-aqueous wetting agents are used.

The patent in suit provided an inventive selection over D3 in that no wetting agent selected from the group of isopropyl alcohol, acetone, ethanol, dichloromethan or mixtures thereof was disclosed, and that this selection provided an improved stability of the moxifloxacin, as disclosed in the patent in suit. In fact, D3 taught away from the avoidance of water when referring to an inert diluent, which could comprise water. It seemt that the opposition division applied hindsight to the analysis in a wet granulation process it is commonly known to avoid water.

The subject matter of claim 1 of the patent in suit thus involved an inventive step in view of D3.

XII. The arguments of the respondent may be summarised as follows:

Admission of auxiliary request 1 into the proceedings

In the auxiliary request, claim 3 had been introduced into claim 1. Such a request based on such an amendment could have been presented in the first instance proceedings and, in line with A. 12(4) RPBA. The patentee had not cited any objective reasons to justify the filing of this auxiliary request at the appeal stage of proceedings.

Inventive step

D3 explicitly disclosed a preferred oral solid preparation is a tablet, which may be prepared by wet

granulation of the crystalline form III of anhydrous moxifloxacin monohydrochloride. A mixture of the powdered compound was moistened with an inert liquid diluent was suitable in the case of oral solid dosage forms

The distinguishing feature between the claimed invention and the disclosure of D3 was the selection of organic solvents as wetting agents in a wet granulation method.

In the absence of a direct comparative test, the claimed selection of organic solvents as wetting agents in a wet granulation method did not appear to provide any special technical effect.

Accordingly, the objective technical problem was considered to be the provision of an alternative wet granulation method.

D3 already taught preparing an oral solid preparation by wet granulation of the crystalline form III of anhydrous moxifloxacin monohydrochloride. D3 provided examples of carriers including sugar alcohols and ethanol, that were particularly suitable and could be used in solid formulations, and represented the common general knowledge of the skilled person in selecting organic solvents as wetting agents in a wet granulation method.

The skilled person would have also turned to D1 given that D1 was concerned with a method for preparing solid dosage forms of gatifloxacin with granulating solution prepared by dissolving povidone and dispersing dimethicone in isopropyl alcohol.

Accordingly, the selection of organic solvents as wetting agents in a wet granulation method was an obvious alternative within the remit of the skilled person, and an inventive step was lacking.

XIII. Requests

The appellant requested that the decision under appeal be set aside, alternatively that the decision under appeal be set aside and that the patent be maintained according to the set of claims filed as auxiliary request 1 with letter dated 3 June 2015.

The respondent requested that the appeal be dismissed.

Reasons for the Decision

1. Main request - Inventive step

1.1 The aim of the invention is to obtain non-convertible solid pharmaceutical formulations of anhydrous moxifloxacin by using wet granulation. Under specific conditions, it is desired that anhydrous moxifloxacin hydrochloride should permanently keep its properties in the course of preparation of formulation and during storage.

1.2 D3 relates to a crystalline form III of anhydrous moxifloxacin hydrochloride, and also to a composition containing said solid moxifloxacin hydrochloride of which at least 80% by weight and preferably at least 99% by weight is in the crystalline anhydrous form (see D3, col. 10, l. 55- col. 11, l. 5; claims 9, 11)). D3 mentions furthermore that the preferred oral solid preparation is a tablet, prepared by direct

compression, wet granulation, or molding, of the active ingredient(s) with a carrier and other excipients in a manner known to those skilled in the art. According to D3, a mixture of the powdered compound moistened with an inert liquid diluent is suitable in the case of oral solid dosage forms, e.g., powders, capsules, and tablets (see D3, col. 12, l. 13-28). Example 5 of D3 discloses the preparation of a granulate of anhydrous moxifloxacin hydrochloride.

- 1.3 According to the appellant, the selection of wet granulation as claimed provides an improved stability of the moxofloxacin. Hence, the problem can be seen as the provision of an improved wet granulation method for preparing anhydrous moxifloxacin tablets by avoiding water.
- 1.4 The solution is a wet granulation method of anhydrous moxifloxacin wherein the wetting agent is selected from group of isopropyl alcohol, acetone, ethanol, dichloromethane or mixtures thereof.
- 1.5 The patent in suit provides one example of a wet granulation of moxifloxacin hydrochloride with respectively isopropyl alcohol, acetone, ethanol and dichloromethane. A X-ray powder diffractogram is provided for each granulate, with the comment that "there is no conversion to moxifloxacin hydrochloride monohydrate". Further X-ray powder diffractograms are provided for moxifloxacin hydrochloride monohydrate (Fig. 1) for the anhydrous moxifloxacin hydrochloride (Fig. 2), for a granulate obtained with a water granulation (Fig. 3) and for granulates obtained through a wet granulation with respectively isopropanol, acetone, ethanol and dichloromethane (cf. Fig. 4-7).

The diffractogram of Figure 3 shows indeed the presence of the monohydrate form of moxifloxacin hydrochloride when granulated with water, which was to be expected.

None of said diffractograms of Figures 4-7 allows however to draw quantitative conclusions as to the amounts of anhydrous moxifloxacin hydrochloride present in the granulates and to the potential presence of monohydrate moxifloxacin hydrochloride, when wet granulated with respectively isopropanol, acetone, ethanol and dichloromethane. Said diffractograms show indeed only the effective presence of the anhydrous form with intensities varying with the used solvent, they do not give any indication as to the amounts or proportions of the anhydrous form present in the granulate and cannot serve to exclude the presence of the monohydrate form in said granulates.

There is therefore no evidence on file that the selection of a solvent selected from alcohol, acetone, ethanol, dichloromethan or mixtures thereof for a wet granulation provides an improvement, in particular over the teaching of D3, which aimed to provide a composition containing said solid moxifloxacin hydrochloride of which at least 80% by weight and preferably at least 99% by weight is in the crystalline anhydrous form .

It is thus not possible to establish to the existence of an improvement over the prior art. Consequently, in the absence of any experimental evidence or arguments establishing a minimum plausibility, the presence of an improvement of a wet granulation process with a solvent selected from isopropyl alcohol alcohol, acetone, ethanol, dichloromethan or mixtures thereof has not

been credibly demonstrated and the technical problem must be reformulated as the provision of an alternative wet granulation process. In view of the information found in the example of the contested patent, the board is convinced that the problem has been plausibly solved.

- 1.6 The solution appears to be obvious, since wet granulation is a common and usual way of preparing granulates which is also explicitly suggested in D3.

Indeed, even if the type of granulation is not explicitly given in said example 5, the teaching of the description of D3 envisages only a wet granulation for the preparation of granulates. The skilled person would in any case avoid the use of water in this case, in view of the main purpose disclosed in D3, i.e. the preparation of an anhydrous final form.

Moreover, the choice of a lower alcohol such as isopropyl alcohol and ethanol, or of another non-aqueous solvent such as acetone or dichloromethane for a wet granulation, is also commonly known and particularly obvious in order to keep the compound anhydrous during the granulation.

The use of the claimed solvents for a wet granulation is also known for instance from D1 which relates to the wet granulation of gatifloxacin with in particular isopropyl alcohol (see par. [0029] or [0043]) or from D2 which relates to the wet granulation of enrofloxacin with ethanol (see par. [0056]).

The claimed solution does thus not appear to be inventive and the main request does not meet the requirements of Article 56 EPC.

2. Auxiliary request 1

2.1 Admission into the proceedings

This request has been filed with the statement of grounds of appeal in response to the decision of the opposition division. The subject-matter of independent claim 1 has been amended by the introduction of former dependent claim 3 and does not present any complexity or shift of the claimed invention. Said dependent claim 3 had furthermore already been commented as to inventive step in the respondent's notice of opposition.

The Board does therefore not see any reason to not admit this request into the proceedings (Article 12(4) RPBA).

2.2 Inventive step

The subject-matter of claim 1 of auxiliary request 1 has been amended by the specification of the salt of moxifloxacin, namely "wherein the anhydrous moxifloxacin salt is hydrochloride".

The same salt of moxifloxacin is however disclosed in the closest prior art D3. Hence, the amendments do not have any incidence on the reasoning and conclusions on inventive step outlined for the main request, which apply mutatis mutandis to claim 1 of auxiliary request 1. No inventive step can therefore be seen as a result of the specification of the salt of moxifloxacin.

Auxiliary request 1 does therefore not meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



S. Fabiani

J. Riolo

Decision electronically authenticated