Internal distribution code:

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

Datasheet for the decision of 2 February 2017

Case Number: T 0565/15 - 3.3.07

Application Number: 04703158.8

Publication Number: 1592401

IPC: A61K9/14

Language of the proceedings: EN

Title of invention:
PROCESS FOR MODIFYING DRUG CRYSTAL FORMATION OF MYCOPHENOLATE SODIUM SALT

Patent Proprietors:
Novartis AG
Novartis Pharma GmbH

Opponents:
Teva Pharmaceutical Industries Ltd.
Accord Healthcare Ltd

Headword:
MYCOPHENOLATE SODIUM SALT/Novartis AG, Novartis Pharma GmbH

Relevant legal provisions:
EPC Art. 100(c), 100(b), 111(1)

Keyword:
Amendments - Main request and auxiliary request 1 (No) - Auxiliary request 2 (Yes)
Sufficiency of disclosure - Auxiliary request 2 (Yes)

Decisions cited:
G 0009/91

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern
Boards of Appeal
Chambres de recours

European Patent Office
D-80298 MUNICH
GERMANY
Tel. +49 (0) 89 2399-0
Fax +49 (0) 89 2399-4465

Case Number: T 0565/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 2 February 2017

Appellant: (Patent Proprietor 1)	Novartis AG Lichtstrasse 35 4056 Basel (CH)
Appellant: (Patent Proprietor 2)	Novartis Pharma GmbH Brunner Strasse 59 1230 Wien (AT)
Representative:	Didelon, Frédéric Novartis Pharma AG Patent Department 4002 Basel (CH)
Respondent: (Opponent 1)	Teva Pharmaceutical Industries Ltd. 5 Basel Street P.O. Box 3190 49131 Petah Tiqva (IL)
Representative:	Greiner, Elisabeth df-mp Dörries Frank-Molnia & Pohlman Patentanwälte Rechtsanwälte PartG mbB Theatinerstraße 16 80333 München (DE)
Respondent: (Opponent 2)	Accord Healthcare Ltd Sage House 319 Pinner Road North Harrow Middlesex HA1 4HF (GB)
Representative:	Best, Michael Lederer & Keller Patentanwälte Partnerschaft mbB

Unsöldstrasse 2
80538 München (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted on 13 January 2015 revoking European patent No. 1592401 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman A. Usuelli
Members: D. Boulois
I. Beckedorf

Summary of Facts and Submissions

I. European patent No. 1 592 401 (based on application No. 04 703 158.8) was granted on the basis of a set of 14 claims.

II. The patent was opposed under Article 100(a) and (b) EPC, on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed, and extended beyond the content of the original application.

III. The appeal by the patent proprietors (hereinafter called appellant) lies from the decision of the opposition division to revoke the patent.
The decision was based on 8 sets of claims filed with letter of 6 October 2014 as main and auxiliary requests 1-5, and filed with letter of 19 November 2014 as auxiliary requests 6 and 7.

The independent claims of the main and auxiliary requests 1 and 2 read as follows:

a) Main request

"1. Process for modifying the crystal habit of an acicular drug crystal wherein the acicular drug substance is a mycophenolate sodium anhydrate modification A, comprising suspending said crystalline drug substance in a methanol/water solvent system in a ratio ranging between 98:2 and 90:10 and subjecting said suspension to a temperature oscillation, wherein the crystal habit is modified in that the mean aspect ratio of the processed crystals is smaller than 10:1 and the bulk density is above 200 kg/m^3."

"2. Process for recrystallising an acicular drug crystal wherein the acicular drug substance is a mycophenolate sodium anhydrate modification A, comprising suspending said crystals in a methanol/water solvent system in a ratio ranging between 98:2 and 90:10 and subjecting said suspension to a temperature oscillation wherein the crystal habit is modified in that the mean aspect ratio of the processed crystals is smaller than 10:1 and the bulk density is above 200 kg/m^3."

"5. Crystals of a mycophenolate sodium anhydrate modification A obtained by a process according to any one of claims 1 to 4 with an aspect ratio smaller than 10:1 and a bulk density of above 200 kg/m^3."

b) Auxiliary request 1

The subject-matter of independent claims 1, 2 and 5 of auxiliary request 1 differed from the corresponding claims of the main request in the specification of the type of salt of mycophenolate sodium, namely: "wherein the acicular drug substance is a mycophenolate **mono-sodium** salt anhydrate modification A".

c) Auxiliary request 2

The subject-matter of independent claims 1, 2 and 4 of auxiliary request 2 read as follows, difference(s) in the auxiliary requests compared with the independent claims of the main request shown in bold:

"1. Process for modifying the crystal habit of an acicular drug crystal wherein the acicular drug substance is a mycophenolate **mono-**sodium salt anhydrate modification A, comprising suspending **fine long rods** of

said crystalline drug substance **having a mean length of 20-50 µm, a mean width of about 1 µm and a bulk density of about 180-200 kg/m^3** in a methanol/water solvent system in a ratio ranging between 98:2 and 90:10 **in a stirred vessel** and subjecting said suspension to a temperature oscillation **at a mean temperature of 44°C with an amplitude of +/- 6°C, with a period of 110 mn per oscillation and a zigzag curve over time, followed by addition of ethanol, cooling to 0°C within 3 hours, filtration and drying in a rotary dryer**, wherein the crystal habit is modified in that the mean aspect ratio of the processed crystals is smaller than 10:1 and the bulk density is above 200 kg/m^3."

"2. Process for recrystallising an acicular drug crystal wherein the acicular drug substance is a mycophenolate **mono-**sodium salt anhydrate modification A, comprising suspending said crystals, **being fine long rods having a mean length of 20-50 µm, a mean width of about 1 µm and a bulk density of about 180-200 kg/m^3** in a methanol/water solvent system in a ratio ranging between 98:2 and 90:10 **in a stirred vessel** and subjecting said suspension to a temperature oscillation **at a mean temperature of 44°C with an amplitude of +/- 6°C, with a period of 110 mn per oscillation and a zigzag curve over time, followed by addition of ethanol, cooling to 0°C within 3 hours, filtration and drying in a rotary dryer**, wherein the crystal habit is modified in that the mean aspect ratio of the processed crystals is smaller than 10:1 and the bulk density is above 200 kg/m^3."

"4. Crystals of a mycophenolate sodium anhydrate modification A obtained by a process according to any one of claims 1 to **3** with an aspect ratio smaller than 10:1 and a bulk density of above 200 kg/m^3."

IV. The documents cited during the opposition proceedings included the following:

D11: Novartis Pharma AG, letter of 19 July 2013, Annex B.: "Protocol for the repetition of the procedure of D4 (Rihs et al.)", pages 1-6

D15: Europaisches Arzneibuch 4. Ausgabe, Grundwerk 2002, Band 1, Seiten 68-69, Kapitel 2.2.42: Dichte von Feststoffen.

D16: WHO Document QA/11.450 Final: "Bulk Density and Tapped Density of Powders. Final text for addition to the International Pharmacopoeia", March 2012, pages 1-6.

D17: US Pharmacopoeia USP25, item 616: "Bulk Density and Tapped Density", 2001, pages 1981-1982.

D18: Declaration of Dr. Wolfgang Schlocker, 02.10.2014, pages 1-6.

D18e: HANCOCK et al PHARMACEUTICAL TECHNOLOGY April 2003, 64-80.

D22: Nürnberg, Surmann (Hrsg.): "Hagers Handbuch der pharmazeutischen Praxis", 5. Auflage, Springer-Verlag, Berlin, 1991, Seiten 45-56.

D23: Declaration of Janos Hajko and Adrienn Kovacs, 02.10.2014, pages 1-15.

D26: European Pharmacopoeia 5.0, 2005, pages 64-65, chapter 2.2.42: Density of Solids.

D27: Bauer at al.: "Pharmazeutische Technologie", 5. Auflage, Gustav Fischer Verlag, Stuttgart, 1997, 301-302.

D28: ASTM D7481-09: Standard Test Methods for Determining Loose and Tapped Bulk Densities using a Graduated Cylinder, 2009, pages 1-4.

D29: Abdullah; Geldart, Powder Technology, 1999, 102, 151-165

V. According to the decision under appeal, all requests complied with Article 123(2) EPC. The feature of "a methanol/water solvent system in a ratio ranging between 98:2 to 90:10" replaced the phrase "a solvent system having an effect on the crystal habit" in original claims 1-2 and was in particular taken from the passage at the end of examples 2-5 at original page 19, lines 13-14. The introduction of the solvent system "methanol/water 98:2 to 90:10" in combination with the "modification A" into the claims was thus an allowable intermediate generalisation of the examples.

The invention was however not sufficiently disclosed. In view of the arguments based on D26 and D22 ,it did not appear plausible that the term "bulk density" was so unambiguously clear that it would always mean "poured" bulk density without tapping. "Bulk density" was also called "apparent density" in view of D26, and according to D22 the equivalent German term was "scheinbare Dichte", which, when translated in English, could mean density after pouring and/or tapping.

Moreover, the term "bulk density" also lacked disclosure because the patent did not describe sufficiently clearly and completely how the value of the bulk density was to be determined. The method of measurement including the sample preparation was very important because the measured value depended on the handling of the bulk material and the measurement method. In this context, D15 stated that the bulk density was often very difficult to determine, it was therefore necessary to specify how the bulk density had been determined (D15, page 69, right column, paragraph 2). This was echoed by D17 which added that the bulking properties of a powder were dependent on the history of the powder, e.g. how it was handled (D17, page 1981,

chapter 616, first paragraph) and by D18e, which stated that results could easily be affected by the choice of equipment, operator technique, or measurement conditions (D18e, page 66, right column, penultimate paragraph). D18 also highlighted that the bulk density was very difficult to determine, as this parameter was affected by the preparation, handling and storage of the substance, in other words by the history of the powder. Therefore, it was generally required that the precise method used for determining the bulk density had always to be quoted together with the parameter value (D18, page 5, point 21). The dependency of the measured bulk density value from the implementation of the measurement method and sample size was illustrated by D23 which reported a measured poured density of 211 kg/m3 for a 20 g sample and 190 kg/m3 for a 2 g sample of the same material (D23, pages 4-5). Consequently, as no information was given in the patent as to how the bulk density was to be measured, the skilled person could not know whether he had succeeded or failed to reproduce the invention as claimed. The opposition division concluded thus that the invention to which the patent related was not sufficiently disclosed.

This conclusion applied to all requests, since all of them referred to the feature "bulk density".

VI. The proprietor (appellant) filed an appeal against said decision. With the statement setting out the grounds of appeal dated 26 May 2015 the appellant requested that the decision of the first instance be set aside and the case be remitted to the first instance to consider the remaining grounds of opposition on the basis of the main request and of the 7 auxiliary requests submitted during the first instance proceedings. It submitted an

auxiliary request 8 and the following items of evidence:
D30: European Pharmacopoeia 8.0 2.9.34 2013
D31: Declaration Dr Edgar John

VII. With a letter dated 9 October 2015, opponent 01 (hereafter called respondent 01) responded to the statement of grounds of appeal and submitted new items of evidence:
D32: Declaration of Dr. Wolfgang Schlocker
D33: Declaration pf Janos Haijko, Ph.D and Sdrienn Kovacs

VIII. A communication from the Board, dated 29 November 2016, was sent to the parties. It was stated in particular that the main request and auxiliary request 1 did not appear to meet the requirements of Article 123(2) EPC, and that auxiliary request 2 appeared to meet the requirements of Article 100(b) EPC.

IX. With a letter dated 2 January 2017, the appellant submitted a new document:
D34: Eur. Pharmacopoiea, 2001, page 58

X. Oral proceedings took place on 2 February 2017, for the course of which reference is made to the minutes.

XI. The arguments of the appellant, as far as relevant to the present decision, may be summarised as follows:

Main request - amendments

The basis for the subject-matter of claims 1 or 2 was original claims 1, 3 and 4. As to the mycophenolate sodium anhydrate modification A, it was the preferred compound disclosed on page 5, lines 10-13 of the

original description. Said modification A was also inherently a mono sodium salt.

A basis for the feature "a methanol/water solvent system in a ratio ranging between 98:2 and 90:10" was found on page 19, lines 13-14 of the original application, after the disclosure of examples 2-5. A skilled reader would have understood that this feature was not restricted to the specific context of said examples, but could be used to characterize the invention and was an independent and general statement. Said feature was not closely associated with the other features of the examples, did not have a clearly recognisable functional or structural relationship with the other parameters in examples 2-5 and was not linked inextricably with further features of examples 2-5. The incorporation of this feature in claim 1 was an allowable intermediate generalization.
A skilled person would not have read lines 13-14 as being tied to any of the process parameters of the example(s), such as the oscillation pattern. Page 4, lines 3-10 of the application taught indeed that oscillation parameters would "depend upon the nature of the solvent or solvent mixture". Lines 13-14 indeed varied the solvent mixture when compared to lines 3-11, so the skilled person would have understood that the alternative range of solvent mixture was clearly not restricted to the same process parameters which had been used with a specific 95:5 mixture.

As to the subject-matter of claim 5, it related to a product by process, and claim 5 depended on claim 1, which meant that its subject-matter was more restricted and had the mean aspect ratio as claimed in claim 1.

Auxiliary requests 1 and 2 - amendments

The same arguments as for the main request applied. The number of oscillations in particular was not essential, and was not linked with the solvent ratio mixture.

Auxiliary request 2 - sufficiency of disclosure

In its decision, the opposition division concluded that the English-language term "apparent density", used as an alternative to "bulk density" in D26, might be interpreted in two different ways if it would first be translated into German ("scheinbare Dichte"). The error in this reasoning was immediately clear, namely that a potential ambiguity in a particular German language term could not be used to create ambiguity in a clear English language term. D22 might have been correct in stating that the term "scheinbare Dichte" was not used consistently in German, but this did not mean that the term "bulk density" was ambiguous in English. The official language of the patent is English, and the evidence showed that the term “bulk density” in this language had only one meaning, so the difference between "Schüttdichte" and "Stampfdichte" in German, or the inconsistent usage of "scheinbare Dichte", was irrelevant. The flaw in this reasoning was that D22 could not be used to modify the unambiguous disclosure of D26 because there was no reasonable link between these two documents.

Moreover, D34 was an extract of the Eur. Pharmacopoeia from 2002, which confirmed that the term "bulk density" could only mean what was intended in the patent.

It was also possible to determine which method was to be used to measure the bulk density. D15 was an extract from the European Pharmacopoeia, which specified that three techniques could be used for determining bulk density. These were described in D30:
(1) using a graduated cylinder;
(2) using a volumeter; or
(3) using a vessel.
The information which D15 described as "essential" was to specify which of these three methods was used (e.g. see final sentence of page 343 in D30), but this information would not have been "essential" if different methods gave the same result for any given sample. In this respect, experimental data in D31 showed that the two favoured methods of Ph. Eur. gave consistent and reproducible bulk density values for the mycophenolate sodium salts of the present claims.

Remittal to the opposition division

The remaining grounds of opposition had not been discussed before the opposition division, the case was therefore to be remitted if the discussion turned in particular to the assessment of novelty and/or inventive step.

XII. The arguments of the respondents, as far as relevant to the present decision, may be summarised as follows:

Main request - amendments

According to respondent 01, there was no basis for combining the methanol/water ratio disclosed in the description, on page 19, with the other features of claim 1. There was a relationship with the other

features of the examples, and it could not be generalized.

According to respondent 01, the claimed subject-matter of claim 5 was also not derivable from the original disclosure, since it was a combination of features of the "crystals of a mycophenolate sodium anhydrate modification A" with "an aspect ratio smaller than 10:1" and "a bulk density of above 200 kg/m^3" not disclosed originally. The description referred furthermore to a "mean aspect ratio" and not the claimed "aspect ratio". The modification A was furthermore only the starting product and not the final product. There was no indication that the modification of the starting material in the examples was preserved during the process. There was no clear and unambiguous disclosure for the subject-matter of claim 6, in view of the combination of the claimed bulk density range of 300 to 60 kg/m^3 with the other features.

According to respondent 02, the solvent ratio feature was technically and functionally linked with the features of the examples and could not be generalized. The recrystallization was dependent on the temperature used and the solvent system used. The oscillation temperature had in particular to be the same as in the examples. As to the passage on page 4 of the description, it expressed that with a specific solvent, the oscillation temperature had to be the same as in the examples. Claim 1 *inter alia* did not specify either the mono sodium salt, or the size of the starting crystals.

Auxiliary requests 1 and 2 - amendments

The same arguments as for the main request applied.

According to respondent 02, not all features from the examples were incorporated in the claims, such as in particular the number of temperature oscillations.

Auxiliary request 2 - Sufficiency of disclosure

According to respondent 01, the meaning of the term "bulk density", and in particular the question whether this term referred to the bulk density determined by the poured bulk density method, or by the tapped bulk density method was not clear. The English version of the European Pharmacopoeia D26 suggested that the term bulk density was also called apparent density. D22 then explicitly stated that the German term "scheinbare Dichte" corresponding to "apparent density" was not uniformly used and could mean bulk density after pouring and/or tapping. It was thus readily derivable that the term "bulk density" was a general term that related to a parameter describing the properties of a powder, i.e., the density of powder particles and the space arrangement of particles in the powder bed.
This parameter was difficult to determine as the slightest disturbance of the bed could result in a new bulk density. Therefore, it was essential in reporting bulk density to specify how the determination was made. Two determination methods A and B for determining the bulk density were then suggested. This showed that the parameter "bulk density" referred to the density of the powder, irrespective which method was used for determining it, and particularly, that this term did not exclusively mean "poured density".
The patent did not provide any guidance how to determine the parameter "bulk density". The conditions under which the bulk density was determined were highly critical and greatly affected the result. This was

confirmed by D26. D26 exemplified two different measuring methods, according to which the bulk density may be determined. The same disclosure was found in the corresponding German document D15 and confirmed by D17, D18 and D18e.
Moreover, the data presented in D23 further evidenced the importance of reporting the exact measuring method and conditions applied. The experiments presented in D23 were reproducible and verifiable and demonstrated that the bulk density of the same material, i.e., mycophenolate sodium of Modification A, was once within the claimed range, and once outside the claimed range depending on the amount of powder used for the bulk density determination.

According to respondent 02, the starting product was also defined by its bulk density range, which, given the unclarity of the parameter and the difficulty to measure it, prevented the skilled person from using an appropriate starting product, and thus implementing the claimed process and obtaining the corresponding final crystals.

Remittal to the opposition division

The respondents objected to the remittal to the first instance, in view of the age of the patent and the delay implied by such remittal. They also considered that there were clear indicators of a lack of inventive step, and that it was not necessary to remit the case to the opposition division.

XIII. Requests

The appellant requests that the decision under appeal be set aside and that the case be remitted to the opposition division for further prosecution on the basis of one of the sets of claims filed with letter of 6 October 2014 as main request and as auxiliary requests 1 to 5, with letter of 19 November 2014 as auxiliary requests 6 and 7, and with letter of 26 May 2015 as auxiliary request 8.

Respondents 01 and 02 request that the appeal be dismissed.

Reasons for the Decision

1. Main request - Amendments (Article 100(c) EPC)

1.1 The subject-matter of claims 1 and 2 as originally filed read as follows:

"1. Process for modifying the crystal habit of an acicular drug substance comprising suspending said crystalline drug substance in a solvent system having an effect on the crystal habit and subjecting said suspension to a temperature oscillation".

"2. Process for recrystallising an acicular drug substance comprising suspending said crystals in a solvent system having an effect on the crystal habit and subjecting said suspension to a temperature oscillation".

1.2 The subject-matter of claims 1 and 2 of the main request has thus been amended *inter alia* by the following feature shown in bold: "comprising suspending said crystalline drug substance **in a methanol/water solvent system in a ratio ranging between 98:2 and**

90:10 and subjecting said suspension to a temperature oscillation".

The only basis for this feature is to be found in a passage on page 19, lines 13-14 of the original description, said passage linking the crystallization examples 2-5 and example 6 relating to the formulation of said crystals in tablets. Said passage reads: "Similarly, the mycophenolate mono-sodium salt may be suspended in methanol/water in another mixing ratio ranging between about 98:2 and 90:10".

The term "similarly" is a clear and direct reference to the process described in examples 2-5, wherein a specific temperature of oscillation of 44°C is used with a specific methanol/water ratio of 95:5, of which kinship with the claimed methanol/water ratio of 98:2 to 90:10 is clear. The methanol/water ratio is therefore technically and functionally linked with the specific process features of the examples and cannot be generalized to the general process features of claims 1 and 2 of the main request.

The description mentions furthermore on page 4, lines 5-10 that "the parameters for the temperature of oscillation depend upon the nature of the solvent or solvent mixture, the nature of the crystals, the desired particle size and/or desired bulk density and may be optimized using standard tests". This passage confirms the close link between at least some process parameters such as the temperature oscillation and the choice of the solvent mixture.

1.3 The subject-matter of claim 1 of the main request is therefore not derivable directly and unambiguously from the application as originally filed, and the main

request does not meet the requirements of Article 123(2) EPC.

2. Auxiliary request 1 - Amendments

The subject-matter of claims 1 and 2 of auxiliary request 1 differs from the subject-matter of corresponding claims 1 and 2 of the main request by specifying the "mono-sodium salt" of the claimed mycophenolate. The amendment relating to the nature of the salt does not affect the conclusions reached above for the main request.

Auxiliary request 1 does not meet the requirements of Article 123(2) EPC.

3. Auxiliary request 2

3.1 Amendments - Article 100(c) EPC

The subject-matter of claims 1, 2, 4 and 5 has been objected to by the respondents.

3.1.1 In comparison to claims 1 and 2 as originally filed, the subject-matter of claims 1 and 2 of auxiliary request 2 has been restricted by features originating from original claims 3 and 4 or from examples 1-6 as follows, with the modifications shown in bold:
a) "wherein the acicular drug substance is **a mycophenolate mono-sodium salt anhydrate modification A**",
b) "comprising suspending **fine long rods** of said crystalline drug substance **having a mean length of 20-50 µm, a mean width of about 1 µm and a bulk density of about 180-200 kg/m^3**"

c) **"in a methanol/water solvent system in a ratio ranging between 98:2 and 90:10 in a stirred vessel"**
d) "subjecting said suspension to a temperature oscillation **at a mean temperature of 44°C with an amplitude of +/- 6°C, with a period of 110 mn per oscillation and a zigzag curve over time, followed by addition of ethanol, cooling to 0°C within 3 hours, filtration and drying in a rotary dryer"**
e) **"wherein the crystal habit is modified in that the mean aspect ratio of the processed crystals is smaller than 10:1 and the bulk density is above 200 kg/m^3."**

Features a) and b) are disclosed directly and unambiguously in example 1 of the application as originally filed, said example relating to the crystals whose habit is modified as described in further examples 2-6.

Features c) and d) are the exact and precise processing conditions disclosed in examples 2-5 with the omission of the number of oscillations and a solvent system with a broader ratio range.

The solvent system used in examples 2-5 is indeed "a methanol/water system in a mixing ratio of 95/5", while the claimed solvent system is **"a methanol/water solvent system in a ratio ranging between 98:2 and 90:10".** Said broader ratio range is disclosed at the end of examples 2-5 on page 19, lines 13-14 as follows:
"Similarly, the mycophenolate mono-sodium salt may be suspended in methanol/water in another mixing ratio ranging between about 98:2 and 90:10". It can be concluded from this passage that the parameter process used in examples 2-5 can be interchangeably associated with the same solvent mixture but in a broader range

ratio to produce the same final product. This generalization is therefore allowable.

As regards the oscillations, the number of oscillations in examples 2-5 varies between 5 and 16, providing a crystal with a minimal bulk density of 280 kg/m^3 with 5 oscillations, and a higher bulk density with a higher number of oscillations. The number of oscillations appears therefore to be the specific process parameter allowing the claimed process to be adapted to obtain a desired bulk density.
In view of the restriction imposed by the wording "the bulk density is above 200 kg/m^3" in claims 1 and 2, the number of oscillations as disclosed in the examples appears to be covered by said wording and both wordings are considered as technically equivalent features. The incorporation of the minimal number of oscillations in claims 1 or 2 is therefore not essential.

Feature e) finds support in original claims 3 and 4, which depended on claim 1.

The subject-matter of independent claims 1 and 2 therefore constitute an intermediate generalization derivable directly and unambiguously from the application as originally filed, especially examples 1-6 of said application.

3.1.2 The subject-matter of independent claim 4 is a product-by-process claim referring to the process of claims 1 or 2. It is also based on the subject-matter of the product claim 7 as originally filed, namely:
"7. Crystals of an acicular drug substance with an aspect ratio of about 10:1 to 1:1 and/or a bulk density of above 200 kg/m^3."

Said subject-matter of claim 4 differs therefore form said original claim 7 by following features, with the modifications in bold:

a) **"a mycophenolate mono-sodium anhydrate modification A"**

b) **"obtained by a process according to any one of claims 1 to 3"**

c) "with an aspect ratio **smaller than 10:1**"

d) "**and** a bulk density of above 200 kg/m^3."

It is immediately apparent that "mycophenolate sodium anhydrate modification A" is the preferred drug substance, since this drug is exclusively used in all examples 1-6 of the application as filed. The specification of the preferred drug substance in the product claim 4 is thus seen as a restriction to the preferred embodiment of the invention and is therefore derivable directly and unambiguously from the application as filed. Moreover, in view of the incorporation of most of the process parameters disclosed in examples 1-6, it is even more obvious that said feature "mycophenolate sodium anhydrate modification A" applies directly and unambiguously to the subject-matter now claimed in auxiliary request 2.

As regards the nature of the drug, the Board could not follow the argumentation of respondent 01, that said modification A was only the starting product and could not be the final product. It is indeed clear that the subject of the invention and of all the claims is a process for modifying the crystal habits or for recrystallising a drug substance, without changing the polymorphic form of the drug. This objection is therefore irrelevant.

Feature b) establishing a product-by-process is a further restriction of the scope of the product claim which is derivable directly and unambiguously from the whole disclosure of the original application.

The limitation of the aspect ratio to its highest range limit, namely "smaller than 10:1" is also derivable directly and unambiguously from the originally claimed range "of about 10:1 to 1:1". The omission of its lower range does not add new technical information, in view of the broadest "mean aspect ratio ... smaller than 10:1" which was claimed by claim 3 as originally filed, and taken up again in claims 1 and 2 of auxiliary request 2 to which claim 4 refers.

Lastly, the combination of the features "crystals of a mycophenolate sodium anhydrate modification A" with "an aspect ratio smaller than 10:1" and "a bulk density of above 200 kg/m^3" is also derivable directly and unambiguously from the original application. It is not possible to see such a combination as the result of multiple selection since all the claimed parameter relate concomitantly to the drug substance and said parameter can not be seen as possible alternative properties of the drug crystals.

The subject-matter of claim 4 is therefore derivable directly and unambiguously from the application as originally filed.

3.1.3 The subject-matter of dependent claim 5 read as follows:
"5. Crystals of a mycophenolate mono-sodium salt anhydrate modification A according to claim 4 with an aspect ratio smaller than 10:1 and a bulk density of 300 to 600 kg/m^3."

Said range of bulk density is disclosed directly and unambiguously in the original description on page 5, line 21.

The subject-matter of claim 5 is therefore derivable directly and unambiguously from the application as originally filed.

3.2 Sufficiency of disclosure - Article 100(b) EPC

3.2.1 In order to fulfil the requirement of sufficiency of disclosure, a patent must contain sufficient information to allow a person skilled in the art, using his common general knowledge, to carry out the invention within the whole area that is claimed.

Sufficiency of disclosure might in particular be questionable if specific values of an unusual parameter are formulated in a patent as essential to the invention but no method of measuring that parameter is either known in the art or disclosed in the patent. It might also be questionable if such specific values refer to a known or usual parameter, when several methods of measurement of said known parameter exist and give incompatible results, independently of the normal standard deviations which might be expected from such measurements, and none of said methods to be used is specified in the patent.

3.2.2 The subject-matter of claims 1 and 2 relates to a process for modifying the crystal habit or for recrystallizing a mycophenolate mono-sodium anhydrate modification A which almost entirely covers the processing parameters and conditions disclosed in examples 1-6, except that it omits the number of

temperature oscillations and the use of a solvent system with a broader ratio range than in said examples, namely a "methanol/water solvent system in a ratio ranging between 98:2 an 90:10" instead of the specific ratio of 95:5 used in the examples. The missing teaching is however clearly given by the examples of the patent, namely a number of temperature oscillations varying between 5 and 16 in the examples, 5 oscillations providing a crystal with a bulk density of 280 kg/m^3. The skilled person would therefore have no difficulty in repeating the processes of claims 1 and 2.

Said crystals of mycophenolate mono-sodium anhydrate modification A are furthermore defined by a specific starting and final "bulk density". This parameter appears therefore to be an essential feature.

Said parameter of "bulk density" is not an unusual parameter, since it was listed in the US and the European Pharmacopoeiae and was recognized as a standard parameter at the priority date of the contested patent by both Pharmacopoeiae, thus before 20.1.2003 (see D17 from 2001 and D34 from 2002).

A clear distinction is furthermore made in both Pharmacopoeiae between the parameters "bulk density" and "tapped density". The Board can therefore not follow the reasoning of respondent 01 also followed by the opposition division in its decision and based on the observation that, according to D26, the bulk density is also called apparent density and according to D22 (in German language) the expression "scheinbare Dichte", i.e. the literal translation of "apparent density", is not uniformly used. In other words, respondent 01 refers to a synonym of the expression

"bulk density", synonym which is never used in the patent in suit, considers the German translation of this synonym, observes that said German translation may have various meanings and concludes that also the original expression may have various meanings. In the Board's view, since the concept of "bulk density" is well recognised by the skilled person (see above), it appears quite illogical to provide alternative interpretations of this concept on the basis of such tortuous reasoning.

Two methods of measurement of said "bulk density" were given by the US Pharmacopoeia (USP) of 2001 (see D17), namely by measurement in a graduated cylinder (Method I) or in a volumeter (Method II). The USP gives furthermore particular minimal requirements for measuring said parameter of bulk density, namely a minimal quantity of 100 g with 0.1% accuracy of the test powder. In the case of a powder with too low or too high density, a sample mass with an untapped apparent volume of 150 to 250 ml of said test powder should be selected, and for test samples having an apparent volume between 50 and 100 ml, a 100 ml cylinder can be used.
The European Pharmacopeia gives in its version of 2002 a method involving a mass measurement of the powder sample in a predefined graduated cylinder (see D34).

Both Pharmacopoeia mention the difficulty of measuring this parameter since the slightest disturbance of the bed may result in a new bulk density. They make clear that the bulking properties of a powder are dependent on the history of the powder, e.g. how it was handled. Consequently, both Pharmacopoeiae emphasize that it is essential in reporting bulk density to specify how the determination was made (see D17 and D34).

The fact that the bulk density is a parameter affected by preparation, handling and storage of the powders, appears however to play a limited role in the present case. There could indeed be a lack of sufficient disclosure in the present case only if the selection of the starting powder on the basis of its bulk density would be impossible in view of unreliable measurement results, or if the determination of the bulk density of the final crystals obtained after the claimed process of claims 1 or 2, presented incompatible or unreliable results when measured by one or more than one known methods, independently from the normal standard deviations which should be expected from such measures.

With the detailed and precise measurement procedures given by the Pharmacopoiea and in the absence of clear evidence to the contrary, there is however no reason to think that such a measurement method cannot be considered as significant and reliable. There is indeed no evidence, in particular no experimental evidence, that a given standard method of measurement of the bulk density chosen among the three existing standard methods and used following said precise instructions at the priority date of the contested patent would lead to a result that would be incompatible with or contradictory to a result obtained with the two other methods, independently from the normal standard deviations which might be expected from such measures. The experiments D31 provided by the appellant show on the contrary a constancy of the parameter measured with different standard methods, with a low standard deviation of 3.6%.

There is also no evidence that repeting the measurement of the bulk density of the mycophenolate with one

specific method by following its instructions would lead to a succession of incompatible results. In this connection, the tests D23 provided by respondent 01 even show the contrary:
- The bulk density of several different powder samples is determined by following the USP Method I in paragraph B2, C, and C2.1; in all tests a cylinder with an apparent volume of 100 ml corresponding to the lowest requirement of the USP was used, probably because of the low density of mycophenolate.
- Two repetitions of the measurement of said "bulk density" of 20 g of mycophenolate mono-sodium anhydrate with the USP Method I in a 100 ml cylinder give respective results of 211 kg/m3 and 212 kg/m3. In the experiments, the powder is poured in a 100 ml cylinder to obtain apparent volume comprised between 50 and 100 ml as a minimum required by the USP, the determination of the bulk density is feasible and gives constant results (see D23 C.2.1).
- Only when the bulk density was determined again for mycophenolate mono-sodium anhydrate by using an amount of powder under the minimal requirements of the USP, namely 2 or 10 g of powder in a 100 ml cylinder, a variation of the measured bulk density was noted, namely respectively 190 kg/m^3 and 183-185 kg/m^3, which the skilled person would have expected in view of the low amount of the powder sample (see D23, C2.2, and D33).

The same constancy of the resulting measurement of the bulk density of mycophenolate when using a standard method is also clearly seen in the experiments D33, also provided by respondent 01.

The skilled person has therefore three standard methods for measuring the bulk density, said methods, in the

absence of any evidence to the contrary, giving compatible and reliable results. There appears thus to be a sufficient disclosure in the patent as regards the parameter of "bulk density".

The invention claimed in claims 1 and 2 of auxiliary request is sufficiently disclosed.

3.2.3 The subject-matter of claim 4 relates to crystals of a mycophenolate sodium anhydrate modification A obtained by a process according to any one of claims 1 to 4 further defined by two parameters, namely with an aspect ratio smaller than 10:1 and a bulk density of above 200 kg/m^3. Dependent claim 5 further specifies the bulk density in a range of 2300 to 600 kg/m3.

Examples 1-6 show the preparation of crystals of mycophenolate mono-sodium anhydrate modification A with a bulk density of at least 280m kg/m3 and having also the aspect ratio as claimed. The results of examples 1-6 are further backed up by the experiments D23 filed by respondent 01, showing the preparation of crystals having the same aspect ratio and bulk density parameters as claimed in claim 4 by a simple grinding process.

The aspect ratio does not present any measurement difficulty, as is confirmed by document D23 provided by respondent 01, which provides said measurement for the powder samples obtained therein (see D23, Tables on pages 7 and 9).

As to the bulk density, this parameter has been already discussed above, with the conclusion that the skilled person had at his disposal three standard methods giving compatible and reliable results.

The invention claimed in claim 4 of auxiliary request is sufficiently disclosed.

3.2.4 None of documents D11, D15, D15, D16, D28, D29 or D30, further mentioned in the discussion on sufficiency of disclosure, has a teaching which can alter the conclusions reached above:
- D16, D26 and D30 are extracts from the European Pharmacopoeia or the International Pharmacopoeia project published after the effective date of the contested patent, which all confirm the teaching of D17 or D34, as does D15, which is the corresponding extract from the European Pharmacopoeia of D34 from 2002 in German, relating to bulk and tapped density, namely explicitly "Schütt- und Stampfdichte" (see page 69);
- D29 provides ASTM standard techniques for measuring the bulk density;
- D28 provides the definition of bulk and tapped density in German ("Schüttdichte", "Stampfdichte")and does not give additional further relevant information;
- D11 is a repetition of the procedure disclosed in D4 and the measurement of the bulk density of the resulting product. The content of this document is irrelevant in the present context.

3.2.5 Consequently, the patent discloses the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

3.3 Remittal

Although Article 111(1) EPC does not guarantee the parties an absolute right to have all the issues in the case considered by two instances, it is well recognised that any party should, whenever possible, be given the

opportunity of such consideration for the important elements of the case. The essential function of an appeal in *inter partes* proceedings is to consider whether the decision which issued by the first instance department was correct. Hence, a case is normally remitted back if essential opposition grounds or questions regarding the patentability of the claimed subject-matter have not yet been examined and decided by the department of first instance. In particular, remittal is considered by the boards in cases where a first instance department had issued a decision based solely on one particular issue which is decisive for the case against a party and leaves other essential issues outstanding. In this respect, the fact that the parties did not submit during the appeal proceedings any new document which might be relevant for assessing an outstanding issue is immaterial.

This is the situation here, since the opposition division has not yet ruled on essential opposition grounds such as novelty or inventive step. Such questions would be raised for the first time during the appeal proceedings, whereas the main purpose of appeal proceedings is to give a losing party the opportunity to challenge the decision of the opposition division (cf. G 9/91, *loc. cit.*, point 18 of the Reasons).

Hence, the Board considers it appropriate to exercise its power under Article 111(1) EPC to remit the case to the opposition division for further prosecution on the basis of the claims according to auxiliary request 2.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division for further prosecution on the basis of the set of claims filed as auxiliary request 2 with letter of 6 October 2014.

The Registrar: The Chairman:

S. Fabiani A. Usuelli

Decision electronically authenticated