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**Datasheet for the decision  
of 1 December 2015**

**Case Number:** T 0571/11 - 3.3.07

**Application Number:** 03722519.0

**Publication Number:** 1501485

**IPC:** A61K9/16, A61K9/26, A61K9/28,  
A61K47/32, A61K47/38,  
A61K31/505

**Language of the proceedings:** EN

**Title of invention:**  
HIGH DRUG LOAD TABLET

**Patent Proprietors:**  
Novartis AG  
Novartis Pharma GmbH

**Opponents:**  
Actavis Group hf.  
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Hightone Management Limited  
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Ratiopharm GmbH  
Zentiva a.s.

**Relevant legal provisions:**

EPC Art. 56, 111(1)

RPBA Art. 12

**Keyword:**

Inventive step - main request (no)

Remittal to the department of first instance - auxiliary  
request (yes)



**Beschwerdekammern**  
**Boards of Appeal**  
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Case Number: T 0571/11 - 3.3.07

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.07**  
**of 1 December 2015**

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**Decision under appeal:** **Decision of the Opposition Division of the European Patent Office posted on 17 January 2011 rejecting the oppositions filed against European patent No. 1501485 pursuant to Article 101(2) EPC.**

**Composition of the Board:**

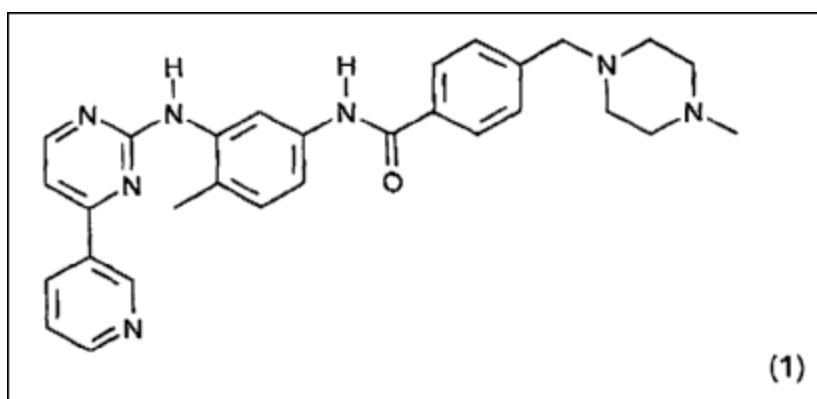
**Chairman** D. Boulois  
**Members:** R. Hauss  
D. T. Keeling

## Summary of Facts and Submissions

- I. European patent No. 1 501 485 was granted with fourteen claims.

Independent **claim 1 as granted** reads as follows:

*"1. A tablet comprising a pharmacologically effective amount of Compound I of formula (1)*



*or a pharmaceutically acceptable salt thereof in an amount from 30% to 80% in weight of the active moiety based on the total weight of the tablet."*

Hereinafter, the term "imatinib" will refer to "Compound I" of the patent in suit, namely 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-(4-pyridin-3-yl)pyrimidin-2-ylamino]phenylbenzamide) (see paragraph [0001] of the patent specification).

- II. The patent was opposed by nine opponents under Article 100(a) and (b) EPC on the grounds that the claimed subject-matter lacked novelty and inventive step and was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.
- III. Opponent 6 later withdrew her opposition.

IV. The documents cited in the course of the opposition and appeal proceedings included the following:

- C1: WO 99/03854 A1
- C3: "Remington: The Science and Practice of Pharmacy", 20th ed. 2000, A. R. Gennaro, Chapter 45
- C4: "Pharmaceutics - The Science of Dosage Form Design", first ed., M.E. Aulton, Churchill Livingstone, 1988, chapters 18 and 39
- C5: "The theory and practice of industrial pharmacy", 2nd ed. 1976, L. Lachmann et al., chapter 11
- C6: "Pharmaceutical dosage forms: Tablets", ed. Lieberman et al., 2nd ed. 1989, volume 1: pages 79-81 and chapters 3-4; volume 2: page 9
- C7: WO 01/47507 A2
- C8: Die Tablette, 2002, pages 64-65
- C10: EP 0 564 409 B1
- C11: EP 0 564 409 A1
- C12: CA 2,093,203 A1
- C49: Approved Text of Package Insert for Gleevec™ (revised 5/9/01) published on 10 May 2001
- C51: K.M. Lee, Current protocols in pharmacology (2001) 7.3.1 - 7.3.10
- C56: Declaration of Dr Michael Gamlen dated 12 September 2010, submitted by opponent 1
- C58: "The Theory and Practice of Industrial Pharmacy", 3rd ed. 1986, Lachmann et al., pages 293-294

V. The decision under appeal is the decision of the opposition division, pronounced on 7 December 2010 and posted on 17 January 2011, rejecting the oppositions.

According to the decision under appeal, the disclosure of the contested patent was sufficient within the meaning of Article 100(b) EPC, since there existed no

serious doubt, substantiated by verifiable facts, that the claimed tablet could not be manufactured or that the invention could not be carried out across the range of drug loadings defined in claim 1, or for particular excipients.

The subject-matter of claim 1 as granted was novel, since the prior-art documents cited against novelty disclosed only tablets containing less than 30% by weight of imatinib (active moiety). Where concentration values within the range of 30% to 80% were disclosed in those documents, that disclosure did not occur in direct and unambiguous association with tablets of imatinib. The subject-matter of the other claims (all referring to the tablet according to claim 1) was also novel.

Inventive step was acknowledged for all granted claims, based on the following considerations: Document C1, and in particular example 4 thereof, represented the closest prior art. The tablet as defined in granted claim 1 differed from the tablet according to example 4 of document C1 in that it contained 30 to 80% by weight of imatinib (active moiety) instead of 22.4% "active ingredient". The benefit linked to that difference was improved patient convenience and compliance, since a single tablet could comprise the total required daily dose, or smaller tablets containing part of a daily dose could be formulated. The objective technical problem was the provision of an oral dosage form improving patient compliance and convenience for administration of the total daily dose of imatinib. That problem was solved across the scope of the claim by tablets incorporating a higher concentration of drug, and that solution was not obvious in view of the available prior art. The prior art, including document C1, taught away from the claimed solution, since the person skilled in the art



would understand from it that the relatively high amounts of excipients used played a functional role in the tablet, and were consequently not optional.

- VI. Opponents 1, 2, 3, 4, 5 and 9 (appellants) lodged appeals against that decision.
- VII. With their reply of 18 October 2011 to the appellants' statements setting out the grounds of appeal, the patent proprietors (respondents) requested that the appeals be dismissed and that the patent be maintained as granted (main request). They furthermore submitted eight auxiliary requests. Remittal of the case to the opposition division, should the board not be able to allow the main request, was also requested.

**Claim 1 of auxiliary request 5** corresponds to claim 1 as granted, but specifies additionally that the tablet comprises cross-linked polyvinylpyrrolidinone from 10% to 35% by weight based on the total weight of the tablet.

- VIII. No written submission was filed in the course of the appeal proceedings on behalf of opponents 7 and 8 (parties to the proceedings as of right pursuant to Article 107, second sentence, EPC).
- IX. With letter of 17 October 2014 third-party observations according to Article 115 EPC were filed, presenting arguments with respect to sufficiency of disclosure, novelty and inventive step.
- X. With letter of 30 October 2015, appellant-opponent 4 presented further arguments and submitted documents C75 (declaration by Sjnezana Miric of 28 October 2015) and C75A (Gleevec<sup>TM</sup> draft package insert revised as of 5 September 2001).

XI. In a communication issued in preparation for oral proceedings, the board *inter alia* gave its preliminary opinion that any of documents C1, C7 or C11 was a suitable starting point for the assessment of inventive step and that, starting from example 8 of C7 (identical to example 4 of C1), the objective technical problem could be formulated as the provision of a tablet comprising imatinib which facilitated patient compliance. Whether the person skilled in the art would seek to produce high drug load tablets as a solution to said problem depended on whether, in view of the prior art and common general knowledge in the field, he would consider it feasible to prepare such a tablet (see section 3 of the board's communication).

Should the respondents' main request not be allowable and remittal of the case for examination of the auxiliary requests still be requested, a decision about remittal would be taken in oral proceedings (see point 4.1 of the board's communication).

The board also observed that the appellants had not yet taken position on the auxiliary requests (see point 5.7 of the board's communication).

XII. Oral proceedings were held on 1 December 2015 with participation of the respondents and appellant-opponents 1, 2, 4 and 9. The representative who appeared for appellant-opponent 4 also represented non-appealing opponent 8 (party as of right), but did not make different submissions on behalf of the latter.

At the outset of the oral proceedings, the respondents withdrew auxiliary requests 1 to 4.

XIII. The appellants'/opponents' arguments may be summarised as follows:

*Main request - inventive step*

The tablet formulation of example 8 of document C7 was a suitable starting point for the assessment of inventive step and differed from the formulation of claim 1 as granted in the concentration of active moiety present in the tablet, calculated as approximately 19% by weight, which fell outside the range of 30 to 80% recited in claim 1. The objective technical problem was the provision of a tablet comprising imatinib which facilitated patient compliance. The solution as defined in claim 1 was obvious in view of the disclosure of document C7 in combination with the common general knowledge of the person skilled in the art. It was a trivial matter to seek to administer the required dose either in smaller tablets, and/or with fewer tablets, by increasing the drug loading.

The common knowledge that the recommended daily dosage of Gleevec™ (imatinib mesylate capsules) was in the range of 400-600 mg imatinib (C49: page 12) provided sufficient motivation to increase the dose and concentration contained in a single tablet. High drug loadings were in any case common in tablets, as shown in table 2/1 of document C8. Tablets were also the typically preferred solid oral dosage form for marketing a drug, due to advantages such as cheap and fast production, small size and robustness (C56: paragraphs 5 to 9; C51: page 7.3.6).

The person skilled in the art was aware of the methods available to prepare a tablet comprising the claimed concentration of active moiety.

While the limits of direct compression with regard to achievable drug load were well known in the art (C3: pages 869-870; C4: page 307; C5: page 334; C6: page 202, table 1; C56: paragraph 27), tablet preparation by direct compression would be considered at drug loadings of 30% (C5) and even up to 50% (C56).

It was also common practice to switch manufacturing techniques depending on the drug load to be achieved, wet granulation being known as the method of choice for preparing tablets with higher drug loads (C6: page 149, page 202: table 1; C56: paragraph 27). There were no credible reasons (such as, for example, moisture sensitivity of the active ingredient) which would discourage the person skilled in the art from preparing a tablet of imatinib using wet granulation, as envisaged in document C11 (example 32).

The respondents' argument that the particle size of the active agent would be considered unsuitably large for wet granulation was irrelevant, since the particle size was not a technical feature of claim 1, and moreover the skilled formulator could always resort to micronisation.

The dissolution properties of imatinib mesylate, known from C49 (page 2, "description"), would not deter the person skilled in the art from attempting to prepare a tablet by a wet granulation method, but rather would guide that person in preparing a tablet which ensured rapid release of the active ingredient by using the appropriate amounts of disintegrant and binder, as was generally known (C4: pages 311 to 312; C5: page 330; C6: pages 173 to 174). Disintegration could be optimised by the choice of appropriate excipients without necessarily reducing the drug load, as argued by the respondents. Moreover, the desired disintegration properties were not even specified in the definition of

claim 1, which therefore also covered tablets with unfavourable disintegration properties.

It was contradictory for the respondents to argue, on the one hand, that imatinib had some specific properties which would prevent the person skilled in the art from increasing the drug load of tablets, while on the other hand the patent specification itself stated that the nature and absolute and relative amounts of the excipients could be chosen by routine experimentation having regard to the desired properties of the tablet, and even its release profile (paragraphs [0017] and [0022] of the patent specification).

Thus the person skilled in the art would think it feasible to prepare high drug load tablets of imatinib or its salts, with a high expectation of success. In this respect, the common general knowledge on tablet formulation would not be dismissed as irrelevant without good reason.

Neither C7 nor any of the documents with similar content cited in the proceedings (C1 and C10) suggested that the imatinib tablets exemplified therein were optimised for full-scale production and could not be modified.

On the contrary, example 8 of C7 could only be seen as illustrative of the invention of C7, and consequently the respondents' argument that the person skilled in the art would interpret it narrowly and restrictively in terms of the ratio of active ingredient to excipients failed. There was no teaching in C7 that the high lactose content disclosed in example 8 was in any way relevant or essential. The tablet of said example was produced using a laboratory scale single punch tablet press - showing that it was purely illustrative -, and the general description of C7 covered single dose forms

comprising up to 90% of the active ingredient (C56: paragraph 45; C7: page 34, paragraph 2).

The potential disadvantages of tablets which were mentioned in document C58 did not apply to imatinib, at least since compressed tablets of imatinib were already known and bioavailability was not an issue in view of the solubility of imatinib.

Finally, the question of whether the development of a capsule would have been a more obvious choice to the person skilled in the art was not relevant to the assessment of whether or not a tablet comprising imatinib in the concentration range claimed involved an inventive step. A developer would in any case focus on tablets, which were usually preferred to capsules as formulations for marketing purposes.

In view of these considerations, the subject-matter of claim 1 of the main request did not involve an inventive step.

#### *Admission of the auxiliary requests*

The subject-matter of the auxiliary requests did not converge within the subject-matter previously claimed, but rather diverged in different directions due to the incorporation of different features in the various requests. Under the established case law, this was not permitted, and the respondents should choose one of the auxiliary requests to present. The remaining requests should not be admitted into the proceedings.

#### *Remittal*

In the statements setting out the grounds of appeal, the appellants had set out clearly their request for revocation of the patent in its entirety. Thus the respondents could not have been taken by surprise, since

they could have expected that the appellants intended to argue against the auxiliary requests. In that respect, the onus remained on the respondents to demonstrate how the newly introduced features solved a technical problem in a non-obvious manner.

The arguments to be advanced were not complicated and relied solely upon evidence already on file. The respondents knew all of the evidence and should be prepared to discuss it. If further evidence were required in defence of the auxiliary requests, it was the responsibility of the respondents to have filed it in time.

In view of those considerations and of the general public interest in bringing the proceedings to a close, remittal to the opposition division should be refused and the board should continue with examination of the auxiliary requests.

XIV. The respondents' arguments may be summarised as follows:

*Main request - inventive step*

The respondents accepted the choice of starting point in the prior art, the difference with respect to granted claim 1 and the objective technical problem as put forward by the appellants. However, the solution to the objective technical problem was not obvious, since the relevant question was not what the person skilled in the art could have done when faced with said problem, but rather what he would have done. Accordingly, the question to be answered was whether the person skilled in the art "would" seek to produce high drug load tablets as a solution to the technical problem.

Neither document C7 nor any other document which could be combined with it prompted the person skilled in the

art to prepare tablets with an increased drug load of imatinib. In particular, the description of C7 (page 34) did not refer to the range of 10 to 90% by weight of active ingredient specifically in association with tablets of imatinib, but only in the context of two more generally defined active ingredients (a) or (b) which could be provided in various different dosage forms, including capsules.

If the preparation of tablets with a high load of imatinib as defined in claim 1 was nevertheless to be considered, the relevant question was whether the person skilled in the art, in view of the closest prior art and the common general knowledge in the field, would have considered it feasible to prepare such tablets with a high expectation of success. Taking into account the known properties of imatinib, combined with the knowledge of the prior-art solid dosage forms thereof, that question had to be answered in the negative.

The limits of direct compression with respect to the amount of active ingredient were well known in the art - problems were usually encountered above 25% by weight active ingredient. Furthermore the prior art did not provide any information regarding the compressibility of imatinib and its salts. Thus the person skilled in the art would *a priori* have considered direct compression methods as unsuitable for producing imatinib tablets with a high drug load.

Although wet granulation was a well-known method for preparing tablets, there were several reasons why the person skilled in the art would *a priori* not consider wet granulation as feasible for producing a tablet comprising a high load of imatinib.

Firstly, as noted in the patent specification (paragraph [0024]), imatinib exhibited a particle size



larger than that typically employed in a wet granulation process. The arguments of the appellants to the effect that the person skilled in the art would simply reduce the particle size to the appropriate range failed, since although he could do it, he would not. Adjusting the particle size was not a trivial matter: in this regard, document C6 (page 199, "B. Concerns", third paragraph) discussed the potential negative effects of particle micronisation and stated that decisions as to whether to granulate a micronised powder should be taken on the basis of *in vivo* blood studies and *in vitro* dissolution tests.

Secondly, it was known from document C49 (page 2) that imatinib mesylate displayed pH-dependent solubility: it was soluble in water and in aqueous buffers at or below a pH of 5.5, but very slightly soluble to insoluble in neutral/alkaline aqueous buffers. Thus it was essential that the active ingredient be released from any tablet formulation quickly enough to allow absorption in the stomach or upper small intestine, thereby avoiding the higher pH environment further along the intestinal tract. Document C6 mentioned that the granulation process was in direct opposition to the principle of increased surface area for rapid drug dissolution (page 198, fourth paragraph) and stated that drug dissolution from tablets prepared by wet granulation was generally slower than for direct compression (table 1, page 202), which went against the requirement of rapid dissolution in the stomach. In this context, the argument of the appellants that the person skilled in the art would simply adjust the amounts of excipients, in particular the disintegrant, to prepare a tablet having the required dissolution profile was inconsistent with the desire of the person skilled in the art to produce a tablet having a high drug load. There would

be little reason for the person skilled in the art to produce a high drug load tablet if it could not be expected to disintegrate at the required rate, and it was consequently irrelevant that wet granulation was a widely used process, when the person skilled in the art would not have expected it to be suitable for a particular active ingredient, viz. imatinib.

No information on additional properties such as compressibility, morphology or particle size distribution were provided in the prior art, properties which the person skilled in the art would need to know before considering whether the preparation of high drug load tablets would be feasible.

The *a priori* expectation of the person skilled in the art that the preparation of tablet with a high load of imatinib would be feasible neither by direct compression nor by wet granulation methods was reinforced by analysis of the compositions of the known dosage forms of imatinib, disclosed *inter alia* in C7.

Imatinib in tablet form was always formulated in the prior art with a high proportion of excipients: The tablet of example 8 of C7 comprised more than 50% crystalline lactose. The person skilled in the art would understand that if so much of one excipient was present, it must play an essential role in the formulation. This was further reinforced by the disclosure of document C12 (identical in subject-matter to documents C10 and C11) in example 32, which described the preparation by wet granulation of a tablet comprising about 14% imatinib and hence a high content of excipients. That disclosure was furthermore in contradiction with the submission of the appellants that the person skilled in the art seeking to produce a tablet containing a high load of imatinib would choose wet granulation to prepare it,

since the tablets of the prior art with the highest loading of imatinib were produced by direct compression, not by wet granulation.

The prior art relating to the preparation of capsules of imatinib was also relevant to the question of inventive step of the tablets, since according to the prior art (C7: examples 9, 10; C12: example 34) whenever a high drug load dosage form was required, capsules were the form of choice.

Furthermore, it was notable that document C58 (page 294) disclosed under "disadvantages" some of the cases in which tablets would not be feasible, including the case of drugs with intermediate or large doses and optimum absorption high in the gastrointestinal tract, and that capsules might offer a more favourable approach.

Thus the person skilled in the art would rationally conclude that the properties of imatinib would make it unsuitable for tablet formulation at a high concentration.

Concluding that the production of high drug load tablets according to granted claim 1 was an obvious measure for solving the technical problem posed amounted to hindsight and upside-down argumentation. For example, only with the benefit of hindsight could it be seen that the high amount of crystalline lactose of example 8 of C7 was not in fact required.

Since the prior art and common general knowledge provided a rational basis for the person skilled in the art to consider as unfeasible the preparation of high drug load tablets in order to solve the objective technical problem, the claimed solution was not obvious and the subject-matter of claim 1 of the main request involved an inventive step.

*Admission of the auxiliary requests*

The auxiliary requests (with the exception of auxiliary request 8) had already been filed before the opposition division. The appellants' objection to the admission of the auxiliary requests had been raised for the first time in oral proceedings before the board of appeal. Given the multiple lines of attack pursued by the appellants, it was equitable for the respondents to be given the opportunity to defend the patent from various angles. Consequently, in view of the requirement for procedural fairness, the requests on file should be admitted into the proceedings.

*Remittal*

The respondents' request that the case be remitted to the opposition division, should the board not be able to grant the main request, had been made with the reply to the statements setting out the grounds of appeal, more than four years before the oral proceedings. The appellants' objection to the remittal had been raised for the first time in oral proceedings before the board and amounted to an amendment to the appellants' case which, in view of Article 13(1) RPBA, should not be admitted at this late procedural stage.

None of the appellants/opponents had previously submitted arguments addressing any issue which might arise in respect of the auxiliary requests.

The tablet as defined in claim 1 of auxiliary request 5 included a particular and unusual concentration level of a specific disintegrant. In terms of that feature, it might be necessary to analyse evidence which had not yet been discussed, and in view of the fact that the respondents did not know the nature of the appellants' arguments, it could not be excluded that the filing of

further evidence or amendments would be required in response.

Public interest needed to be balanced with the principle of procedural fairness. In the present case, the appellants should have properly argued their case before oral proceedings by submitting arguments against the auxiliary requests.

In view of those considerations, it was equitable to remit the case to the opposition division to avoid a situation in which the appellants presented arguments for the first time in oral proceedings for which they had had four years to prepare, while the respondents had not had any time to prepare a response and had to improvise and counter-argue on the spot, a situation which would amount to a violation of the right to be heard enshrined in Article 113(1) EPC.

- XV. The appellants (opponents 1 to 5 and 9) and opponent 8 (party as of right) requested that the decision under appeal be set aside and that the patent be revoked. In addition, appellant-opponent 1 requested that the case not be remitted to the opposition division, should the question arise. Appellant-opponent 2 requested that the auxiliary requests not be admitted into the proceedings.
  
- XVI. The respondents (patent proprietors) requested that the appeals be dismissed and the patent maintained as granted (main request) or, in the alternative, that the case be remitted to the opposition division for further prosecution or, in the further alternative, that the patent be maintained in amended form on the basis of one of the sets of claims filed as auxiliary requests 5 to 8 by letter of 18 October 2011.

The respondents also requested the board not to admit into the proceedings:

- the submissions filed by appellant-opponent 4 on 30 October 2015, and the attached documents;
- the observations filed by a third party under Article 115 EPC on 17 October 2014;
- the request of appellant-opponent 1 for the case not to be remitted to the opposition division.

XVII. Opponent 7, which is a party as of right pursuant to Article 107, second sentence, EPC, did not file any requests or submissions during the appeal proceedings.

## **Reasons for the Decision**

1. Main request - inventive step

### *Patent in suit*

1.1 The patent in suit aims to provide commercially acceptable dosage forms of imatinib for oral administration with good patient convenience and acceptance (see paragraph [0023] of the patent specification).

### *Starting point in the prior art*

1.2 While preferences for documents C1, C7 or C11 were expressed in the written proceedings, all parties considered example 8 of document C7 (identical to example 4 of document C1) to be a suitable starting point for the assessment of inventive step.

1.3 Document C7 relates to combination therapy employing a receptor tyrosine kinase inhibitor (a) and a compound capable of binding to  $\alpha_1$ -acidic glycoprotein (b) in the

treatment of proliferative diseases. Such treatment may involve oral dosage forms containing only one of components (a) and (b), preferably in concentrations between 10% and 90%. Component (a) may be imatinib or one of its salts, in particular mesylate (C7: claim 5; page 4, lines 10 to 14; page 34, second paragraph).

Example 8 of document C7 discloses tablets consisting of 100 mg imatinib monomesylate, 240 mg crystalline lactose, 80 mg microcrystalline cellulose (Avicel), 20 mg cross-linked PVP, 2 mg Aerosil and 5 mg magnesium stearate. The tablets are prepared by mixing the active substance with carrier materials and compressing the mixture on a tableting machine by direct compression (Korsch EKO, punch diameter 10 mm).

*Technical problem and solution*

- 1.4 It is undisputed that the tablet according to claim 1 as granted differs from tablets according to example 8 of document C7 in the concentration of the active moiety, which ranges from 30% to 80% by weight based on the total weight of the tablet according to claim 1, and amounts to approximately 19% according to example 8 of C7.
- 1.5 It was known that the recommended daily dose of imatinib was in the range of 400 to 600 mg imatinib (C49: page 12) and would thus provide a certain bulk of solid powder.
- 1.6 During oral proceedings it was accepted by all parties that the objective technical problem underlying claim 1 could be seen as the provision of a tablet comprising imatinib which facilitated patient compliance.
- 1.7 That problem is solved by the tablet defined in claim 1 as granted, since by producing a tablet having a higher

proportion of imatinib in comparison to the tablets of C7, smaller tablets may be administered compared to prior-art tablets comprising the same dosage (thus making them easier to swallow), or a higher dosage can be provided in a tablet of acceptable size (thus reducing the number of tablets required to administer a specific dose), or a combination of both. It is credible and reasonable to assume that such tablets will facilitate patient compliance in comparison to the imatinib tablets of C7.

*Obviousness of the solution*

1.8 Faced with the aforementioned technical problem, it is in principle straightforward and routine for the person skilled in the art to seek to administer the required dose either in smaller tablets and/or with fewer tablets, by increasing the drug load. For instance, document C8, which is a textbook on tablet development, mentions that in the case of tablets which are to be swallowed it will generally be the aim of the formulator to achieve small tablet sizes. For amounts of 100 mg and more active ingredient per tablet, typical drug loadings are well over 30% by weight (C8: page 64, last complete paragraph and page 65: table 2/1).

In answering the question of obviousness, the respondents conceded that, at the priority date of the patent in suit, the person skilled in the art could have prepared tablets having a high drug load as specified in claim 1, using known techniques and excipients. They argued, however, that that solution would not have been considered feasible due to certain technical facts concerning the properties of imatinib and the known solid dosage forms thereof, and therefore would not have been attempted. The appellants maintained that, in the absence of any credible reasons to the contrary giving



rise to a prejudice, the person skilled in the art would have attempted to prepare high drug load tablets with a reasonable expectation of success, in order to solve the technical problem.

Thus the question of whether the person skilled in the art would have sought to produce tablets containing a high concentration of imatinib (active moiety) as a solution to the technical problem must be answered by determining whether, in view of the prior art and the common general knowledge in the field, it would have been considered feasible to prepare such a tablet.

- 1.9 In the following, each of the respondents' arguments to the effect that the person skilled in the art would not have regarded the preparation of high drug load imatinib tablets as feasible (the "could but would not" argument; see points 1.10, 1.12, 1.14 below) will be considered in turn (see points 1.11, 1.13, 1.15 below).
- 1.9.1 The hypothetical feasibility assessment by the person skilled in the art was invoked by the respondents in the context of obviousness of the subject-matter of claim 1 of the main request. The feasibility assessment relates accordingly to the envisaged solution to the technical problem as defined by the technical features of claim 1. It follows that further limitations which are not reflected by technical features of claim 1 cannot be taken into account in this regard.
- 1.10 *A priori assessment of the feasibility of preparing high drug load tablets*

The respondents argued, in a first point, that the person skilled in the art would *a priori* have considered neither direct compression nor wet granulation methods to be feasible for producing tablets containing a high

load of imatinib or its salts, for the following reasons:

a) Direct compression was known to be unsuitable for the incorporation of high drug loads, and the available prior art did not provide any information about the compressibility of the active ingredient.

b) As far as methods involving wet granulation were concerned,

b.1) the particle size of the active ingredient was too large for wet granulation (as mentioned in the patent in suit in paragraph [0024]), and

b.2) the use of granulated material was known to be unfavourable if rapid dissolution (as required in the case of imatinib) in combination with a high drug load was to be achieved.

Furthermore,

c) since the prior art cited did not disclose any data about properties of the active ingredient such as compressibility, morphology and particle size, the feasibility of preparing high drug load tablets could not be assessed.

1.11 With regard to the arguments under point 1.10, the board does not reach the same conclusion, for the following reasons:

1.11.1 To begin with, while the method of preparation is not defined as an actual technical feature of claim 1, the respondents' argument that the conventional methods of tablet preparation (direct compression and compression after wet granulation) would not have been regarded as feasible in the particular case of high load imatinib tablets is nevertheless taken into account, as it might be argued that alternative "unconventional" methods of

preparation would not automatically be considered feasible. It is implicit that the claimed tablets have to be prepared to be available. Thus the respondents' first argument amounts to saying that at the priority date, the solution to the technical problem (i.e. providing tablets containing a high load of imatinib, by preparing such tablets) would not, in an initial assessment, have been regarded as feasible by the person skilled in the art.

1.11.2 re 1.10.a) - direct compression

The common general knowledge with regard to drug loads achievable with direct compression methods is reflected in various textbooks on pharmaceutical dosage forms (C3 to C6) and in the declaration C56.

It was thus well known that direct compression may pose problems for high dose drugs with respect to compressibility (C6: page 202, table 1) and that the amount of drug which can be tableted using a direct compression method is, in general, limited to 25% or to 30%, unless the drug itself is easily compressible (C4: page 307, right-hand column, second paragraph; C3: page 870, left-hand column, second full paragraph; C5: page 334, left-hand column, point 2).

This general understanding is confirmed by the formulation scientist Dr Gamlen in his declaration C56 (paragraph 27), stating that *"the drug loadings beyond which direct compression becomes problematic, and wet granulation is preferred, range from 15-25%"*.

The statement continues, however, as follows:

*"In my opinion these figures are somewhat low; in companies which preferred direct compression I would expect consideration to be given for direct compression at drug loadings up to 50% although this would depend on the compressibility and bulk density of the active*

*ingredient. When the formulator knows that the proposed drug load is high, the first consideration would be to use the wet granulation method."*

Thus it was known that the upper limit of active ingredient which can be incorporated is not necessarily always below 30% (for example, according to C5 and C56, it may be 30% or higher depending on the individual case). Furthermore, the upper limit was not known to be below 30% in the specific case of imatinib and its salts. The board considers therefore that, contrary to the respondents' view, it would not have been excluded *a priori* at the priority date of the patent that tablets comprising drug loads at least in the lower part of the claimed range could be made by direct compression - it was simply not known whether that was the case.

However, even if the person skilled in the art had ruled out direct compression altogether, the following remarks concerning wet granulation (point 1.11.3) would apply.

#### 1.11.3 re 1.10.b) - wet granulation

Aware of the limitations mentioned above and reasoning that at least part of the envisaged range for drug load might not be accessible by a direct compression method, the person skilled in the art would also have considered whether an appropriate alternative process existed for producing a tablet having a drug load in the upper part of the claimed range, and/or over the entire range of 30 to 80% by weight. In view of the common general knowledge, it would have been immediately apparent that wet granulation, followed by compression of a mixture comprising the granulated material, was the method of choice in this regard.

Thus, according to document C3, wet granulation was the most widely used method of tablet preparation, whose popularity was due to the greater probability that the

granulation would meet all the physical requirements for the compression of good tablets (C3: page 865, right hand column, first paragraph under "Wet Granulation").

Document C6 describes wet granulation as the oldest and most conventional method of making tablets and states that *"In wet granulation, the bonding properties of the liquid binders available is usually sufficient to produce bonding with a minimum of additives"* (C6: page 149, lines 1 and 9 to 11). C6 furthermore mentions that *"Drugs having a high dosage and poor flow and/or compressibility must be granulated by the wet method to obtain suitable flow and cohesion for compression. In this case, the proportion of the binder required to impart adequate compressibility and flow is much less than that of the dry binder needed to produce a tablet by direct compression"* (C6: page 149, point B.2; see also page 151: lines 30 to 33).

The general understanding that wet granulation was the method of choice for producing high drug load tablets is shared by the formulation scientist Dr Gamlen in his declaration C56 (paragraphs 19, 27 and 49).

re 1.10.b.1) - particle size

The statement in the patent in suit regarding particle size (paragraph [0024] of the patent specification), cited by the respondents, reads as follows:

*"More specifically, the tablets of the invention may be prepared by granulation, preferably wet-granulation, followed by compression methods. Compound I, especially the mesylate salt, exhibits high particle size, e.g. 60% of the Compound I starting material having a particle size greater or equal to 100  $\mu\text{m}$ , e.g. 90% of the particles are smaller or equal to 420  $\mu\text{m}$ . Wet-granulation process is usually performed with a starting material of particle size lower than 100  $\mu\text{m}$ ."*

The board considers that the particle size of the active ingredient cannot be of relevance to the assessment by the skilled person of the feasibility of wet granulation for preparing tablets with a high load of imatinib, because claim 1 does not define a particle size (see point 1.9.1 above). Nor is there any reason to assume that particles of imatinib or any of its salts inherently have certain particle sizes. The above-cited statement in the patent specification, mentioning certain materials by way of example (as indicated by the expression "e.g."), does not support such a generalised assumption. Thus the person skilled in the art would not have assessed a specific particle size, but would have been free to consider any suitable particle size.

Small particle sizes were routinely available via micronisation, if required. Contrary to the respondents' argumentation, this common knowledge is indeed confirmed in document C6, stating on page 199 that many drugs are commonly micronised. The known concerns about decreased powder fluidity or compressibility apply to direct compression methods, not to methods involving wet granulation.

re 1.10.b.2) - release properties

Based on the solubility of imatinib mesylate disclosed in document C49 (page 2, "Description") the respondents argued that the claimed tablet must be capable of releasing the drug high in the gastrointestinal tract where pH conditions are optimal for absorption of the drug, but the person skilled in the art would not have considered it feasible to produce such a tablet, having both the claimed imatinib content and the desired release properties, by wet granulation.

Yet claim 1 is not restricted to tablets comprising the mesylate salt of imatinib and does not define any

technical feature relating to gastrointestinal absorption. A contradiction arises also between this line of the respondents' argumentation and the statement in the patent specification itself that a tablet may be chosen to exhibit accelerated and/or delayed release (paragraph [0022]). Thus it cannot be confirmed that immediate release and absorption of the active ingredient are properties which are reflected in the technical features of claim 1 and which would be relevant over the entire scope claimed (see point 1.9.1 above). The respondents' argument must therefore fail.

1.11.4 re 1.10.c) - unknown properties of active ingredient

The respondents' argument that the person skilled in the art would not consider the preparation of high drug load tablets as he was not aware of the properties of imatinib, in particular its compressibility and morphology, does not stand up to scrutiny. Firstly, if information was missing about parameters deemed to be crucial, it does not follow that the skilled person would conclude that the desired tablets could not be prepared. Secondly, even if it had been disclosed in the prior art that imatinib or a particular salt of imatinib was a poorly compressible substance, or that a certain morphology gave rise to unfavourable flow properties, this would not appear to be a decisive issue when the tablet is prepared by wet granulation, a method which can routinely be tailored to overcome precisely such deficiencies (see for example C6: page 202, table 1, "compressibility"; page 149, section B.1).

1.11.5 Consequently, it is not apparent from the respondents' arguments why the person skilled in the art would not *a priori* consider it feasible to prepare tablets with a high load of imatinib conforming to the definition of

claim 1, in particular by turning to the well-known option of wet granulation.

1.12 Teaching of the prior art relating to solid dosage forms of imatinib

The respondents further argued that it would be inferred from the prior art relating specifically to dosage forms of imatinib (represented by C1, C7 and C12) that tablets were not a suitable dosage form for high drug load delivery of imatinib.

a) Only much lower drug loads than 30% were taught in the prior art in association with tablets:

a.1) Crystalline lactose was present at more than 50% of the total tablet weight in formulation example 8 of C7 (corresponding to example 4 of C1). The person skilled in the art would understand that if so much of one excipient was present, it must play an essential role in the formulation, e.g. it might be required for compression, or to mask an unwanted physical property of the active ingredient.

a.2) That assumption was corroborated by the composition of prior-art tablets obtained by wet granulation, which contained an even higher proportion of excipients combined with a drug load of only 14% by weight (C12: example 32). Thus the prior art used even wet granulation only for low drug loads and thereby taught away from the claimed invention.

b) High drug loads were disclosed in the prior art only in association with capsule formulations (C7: examples 9 and 10; C12: example 34), which further reinforced the skilled person's perception that tablets were unsuitable as a dosage form for large concentrations of imatinib or salts thereof.



1.13 With regard to the arguments under point 1.12, the board does not reach the same conclusion, for the following reasons:

1.13.1 re 1.12.a) - prior-art tablets

re 1.12.a.1) - obtained by direct compression

Document C7 does not contain any teaching describing the excipient content in example 8 as essential. The board therefore sees no reason why the person skilled in the art would make such an assumption. Rather, the level of excipients would be considered as typical in the context of the direct compression process applied to the preparation of the tablet which, as discussed above, was known to have limitations in terms of the maximum amount of active ingredient which could be employed. As pointed out by the appellants, it also cannot be excluded that the large proportion of lactose used in example 8 of C7 is simply due to the tablet size which could be produced with the laboratory scale single punch tablet press in which the tablet was prepared. Furthermore, the description of C7 does not comprise any explicit or implicit teaching to the effect that the proportion of excipient present in the examples is to be understood as fixed or optimised. On the contrary, the description indicates that the compositions of the invention may comprise from approximately 10% to approximately 90% of the active ingredient, component (a) or (b) (page 34, first full paragraph). While different dosage forms are possible and this statement does not refer to tablets specifically, C7 does not define a narrower range for tablets either. With respect to excipients, no specific limitations, not even concentration ranges, are proposed (C7: page 34, second full paragraph).

re 1.12.a.2) - obtained after wet granulation

With respect to the disclosure of document C12, example 32 concerns the preparation of "tablets comprising 20 mg of active ingredient, for example one of the compounds of formula I described in Examples 1 to 31" which are "prepared in a customary manner". The synthesis of imatinib is disclosed in example 21. Thus it is difficult to conclude with any level of certainty that the composition described was actually prepared with imatinib as the active ingredient, and was not merely illustrative of the form that a composition may take. Furthermore, C12 is mainly directed to the protection of the active compounds *per se*, such that the person skilled in the art would not understand example 32 as being in any way limitative with respect to the proportion of active ingredient that may be included in a tablet, to the extent that he would consider it optimised and not adjustable. Consequently the respondents' argument according to which this example demonstrated that wet granulation was not suitable for tablets containing a high load of imatinib, since the highest tablet loading of imatinib disclosed in the prior art is produced by direct compression, not wet granulation, must also fail.

In view of these considerations, the person skilled in the art would not have construed the examples of the prior art which were specifically directed to imatinib tablets as limitative with respect to the proportion of imatinib which may be present in the tablet.

1.13.2 re 1.12.b) - prior art capsules

The fact that capsule formulations having higher drug loads are disclosed in the prior art (C7: examples 9 and 10; C12: example 34) is not surprising, since

capsules are generally easy to formulate and known to be suitable for any drug load. This is the reason why capsules are typically used in early clinical studies, prior to the development of tablets as the more typical commercial dosage form (C51: 7.3.6). The disclosure of the above-mentioned capsule formulations has however no relevance for the skilled person's assessment concerning the feasibility of preparing high drug load tablets.

1.14 Disadvantages of tablets

In an additional argument, the respondents referred once more to the common general knowledge as reflected in the prior art, pointing out that document C58 (page 294) disclosed under "disadvantages" some of the cases in which tablets would not be feasible and that capsules might offer the best and least expensive approach. One of them was the case of drugs with intermediate or large doses and optimum absorption high in the gastrointestinal tract, features which might render the tablets difficult or impossible to formulate and manufacture with adequate or full drug bioavailability.

1.15 With regard to the arguments under point 1.14, the board observes that none of the potential disadvantages of tablets mentioned on page 294 of document C58 were known or have been shown to definitively apply to imatinib or its salts; moreover, although C58 mentions potential difficulties it does not, in fact, exclude feasibility. The remark concerning capsules is not relevant to the feasibility of preparing high drug load tablets. Thus the disclosure of C58 is not pertinent.

1.16 It follows that none of the reasons submitted by the respondents would give rise to an expectation of failure, or a prejudice, which would discourage and prevent the skilled person seeking to solve the

objective technical problem from carrying out the obvious solution of preparing tablets having a high drug load of imatinib active moiety, as defined in claim 1. Thus the board concludes that the skilled person would indeed prepare such tablets in order to solve the technical problem.

1.17 As a consequence, the subject-matter of claim 1 of the patent in suit does not involve an inventive step within the meaning of Article 56 EPC.

2. Admission of auxiliary request 5 - Article 12 RPBA

2.1 Like all pending auxiliary requests, auxiliary request 5 was submitted with the respondents' reply to the statements setting out the grounds of appeal (see point VII above). Pursuant to Article 12(1), 12(2) and 12(4), second half-sentence, RPBA, the request is thus to be taken into account in the appeal proceedings.

2.2 The board has however the power to hold inadmissible requests which could have been presented or were not admitted in the first-instance proceedings (see Article 12(4), first half-sentence, RPBA).

2.2.1 As pointed out by the respondents, auxiliary request 5 was in fact presented during the first-instance proceedings (see auxiliary request 5 filed with letter dated 7 October 2010). Furthermore, the opposition division did not take a decision not to admit that request.

2.2.2 Hence the criteria set out in Article 12(4), first half-sentence, RPBA are not met, and the board has no reason not to take auxiliary request 5 into account.

- 2.3 The choice of a single auxiliary request suggested by the appellants is already implicit in auxiliary request 5, since it is the order of the requests which defines the ranked preferences of the proprietors. The objection in respect of the alleged divergence of the auxiliary requests could only be of potential relevance with respect to any subsequent auxiliary requests (provided they were not presented or admitted in the first-instance proceedings).
3. Remittal - Article 111(1) EPC
- 3.1 Since the respondents requested remittal of the case to the opposition division (see point XVI above), and since under Article 111(1) EPC the board may either remit the case or decide on the case, a discretionary decision on remittal must be taken in this situation, irrespective of the appellants' requests in that regard. Hence the respondents' further request, viz. not to admit the appellants' objection to a remittal, has no procedural relevance.
- 3.2 Although the EPC does not guarantee the parties an absolute right to have all the issues of a case considered by two instances, it is well recognised that any party may be given the opportunity of two readings of the important elements of a case. The essential function of an appeal is to consider whether the decision issued by the first-instance department is correct. Hence, a case is normally referred back if essential questions regarding the patentability of the claimed subject-matter have not yet been examined and decided by the department of first instance.
- 3.3 While this typically applies when a first-instance department issues a decision against a party solely upon

some issues which are decisive for the case and leaves other essential issues outstanding, remittal is equally to be considered in a case like the present one, in which the board finds that the decision is not correct and a new issue, even related to the same ground, arises for the first time in appeal.

- 3.4 In the present case, since the opposition division came to the conclusion that the subject-matter of claim 1 of the claims as granted (the main request) involved an inventive step, the arguments in respect of the added technical feature which distinguishes claim 1 of auxiliary request 5 from the subject-matter of claim 1 of the main request (see point VII above) have not been considered at all by the opposition division.
- 3.5 Furthermore, despite the fact that auxiliary request 5 and the request for remittal were filed with the reply to the statements setting out the grounds of appeal, i.e. more than four years before oral proceedings before the board, none of the appellants/opponents has provided further written arguments about them. As a consequence of non-remittal, therefore, the respondents would be placed in an inequitable position compared to the appellants during oral proceedings in that they would be required to respond to the arguments of the appellants/opponents with little or no time to prepare, while in contrast the appellants/opponents had the time from the filing of the auxiliary request. Without actually entering into examination of auxiliary request 5, it cannot be excluded that the discussion would require new issues or approaches to be considered.
- 3.6 While the board recognises the public interest in the timely resolution of the case, this cannot override the need for procedural fairness. The responsibility was

with the appellants to take a position on the auxiliary requests such that the respondents would have had adequate time to prepare a reply and/or to formulate counter-arguments.

- 3.7 In view of the these considerations, the board has reached the conclusion that, in the circumstances of the present case, it is appropriate to remit the case to the opposition division for further prosecution.
4. In view of these findings, a decision on the admission of the third-party observations of 17 October 2014 and the submissions of 30 October 2015 is not required.

## 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.

The Registrar:

The Chairman:



S. Fabiani

D. Boulois

Decision electronically authenticated