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Datasheet for the decision of 20 December 2024

Case Number: T 0356/22 - 3.3.07

Application Number: 18160247.5

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IPC: A61K9/48, A61K31/454, A61K47/26, A61K47/36

Language of the proceedings: EN

Title of invention:
FORMULATIONS OF 4-AMINO-2-(2,6-DIOXOPIPERIDINE-3-YL)ISOINDOLINE-1,3-DIONE

Patent Proprietor:
Celgene Corporation

Opponents:
Pruß, Timo
HGF Limited
Generics (UK) Ltd
Hoffmann Eitle

Headword:
Pomalidomide formulations / CELGENE

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:
T 1193/18, T 2342/19, T 2200/17, T 1126/19

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Case Number: T 0356/22 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 20 December 2024

Appellant: (Opponent 1)	Pruß, Timo Lothringerstraße 33 41462 Neuss (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Appellant: (Opponent 4)	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastrasse 30 81925 München (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Respondent: (Patent Proprietor)	Celgene Corporation Route 206 & Province Line Road Princeton, NJ 08543 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Party as of right: (Opponent 2)	HGF Limited 1 City Walk Leeds Yorkshire LS11 9DX (GB)
Representative:	HGF HGF Limited 1 City Walk Leeds LS11 9DX (GB)

Decision under appeal: **Interlocutory decision of the Opposition Division of the European Patent Office posted on 20 December 2021 concerning maintenance of the European Patent No. 3351240 in amended form.**

Composition of the Board:

Chairman A. Usuelli
Members: E. Duval
A. Jimenez

Summary of Facts and Submissions

I. The appeals were filed by opponent 1 (appellant O1) and opponent 4 (appellant O4) against the interlocutory decision of the opposition division finding that, on the basis of the main request with claims filed on 8 September 2021, the patent in suit met the requirements of the EPC.

II. Claim 1 of the main request read as follows:

"A pharmaceutical dosage form comprising: (i) pomalidomide, or a pharmaceutically acceptable stereoisomer, salt, solvate, hydrate, or clathrate thereof; and (ii) mannitol and starch."

III. The following documents are relevant:

D1: US 2007/0155791 A1
D4: Declaration by Anthony Tutino, 14 June 2013
D16: Adeyeye MC et al: "Preformulation in Solid Dosage Form Development", 2008 pages 347-372

IV. Regarding inventive step, the opposition division reasoned that, starting from D1, the differentiating feature of claim 1 of the main request was that the claimed dosage form comprised mannitol and starch. The technical problem was the provision of a stable dosage form comprising pomalidomide. The claimed solution involved an inventive step.

V. Appellant O1 filed the experimental report D31 with their statement setting out the grounds of appeal, and

later filed, on 16 August 2022, an updated version thereof D31a.

VI. With their reply to the appeals, the patent proprietor (respondent) defended their case on the basis of the main request upheld by the opposition division, and of auxiliary requests 1-41 pending before the opposition division, as well as amended versions thereof (namely amended main request' and auxiliary requests 1'-41').

The amendments carried out in claim 1 of auxiliary requests 1-41 were:
- the limitation to oral pharmaceutical dosage forms, or to oral dosage unit form selected from tablets, caplets, and capsules, and/or
- the addition of the feature that the mannitol and starch comprise 70-99 wt%, 90-99 wt% or 95-99 wt% of total weight of the pharmaceutical dosage form, and/or
- the limitation to a mannitol : starch ratio of from 1:1 to 1:1.5;
- in other auxiliary requests, claim 1 was identical to claim 1 of the main request.

VII. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VIII. Oral proceedings were held before the Board in the presence of appellant O1 and of the respondent. In the course of these oral proceedings, the respondent withdrew the amended main request' and amended auxiliary requests 1'-41'.

IX. The parties' final requests were the following:

(a) Appellant O1 and appellant O4 both request that the decision under appeal be set aside and that the patent be revoked in its entirety.

(b) The respondent requests that the appeals be dismissed and the patent be maintained according to the main request upheld by the opposition division, or, alternatively, that the patent be maintained based on one of auxiliary requests 1-41 pending before the opposition division. The respondent further requests that neither D31 and D31a be admitted into the appeal proceedings.

X. The arguments of the appellants may be summarised as follows:

The closest prior art D1 disclosed a tablet comprising not only pomalidomide (see e.g. claims 2 and 22) but also a filler such as starch (see paragraph [0124] and example 7). The subject-matter of claim 1 differed from D1 merely in that the claimed tablet contained mannitol. Since D4 did not allow a comparison with the closest prior art, the problem could not be seen as the provision of a pomalidomide dosage form that was more stable than the one disclosed in D1. The effect of obtaining a stable formulation was not achieved over the entire claim scope either. Hence the objective technical problem was merely the provision of an alternative pomalidomide oral dosage form. D1 suggested using mannitol, starch, and mixtures thereof, as filler. The claimed solution was thus obvious in view of D1 alone.

XI. The respondent's arguments may be summarised as follows:

The closest prior art D1 did not disclose any pomalidomide-specific formulation, let alone any stable pomalidomide-specific formulation, nor a carrier system that is starch and mannitol. The differentiating feature was the triple combination of pomalidomide, starch, and mannitol. The application as filed explained that the claimed formulations had adequate stability for clinical and other uses, which was also supported by D4. The objective technical problem was the provision of a stable dosage form of pomalidomide suitable for clinical use. The appellants had provided no data showing any unstable formulations of pomalidomide. The claimed solution was inventive because none of the cited prior art provided any teaching that a stable and clinically useful formulation of pomalidomide would be possible by combining pomalidomide with a combination of starch and mannitol.

Reasons for the Decision

1. Main request, inventive step

1.1 According to the patent, the invention seeks to provide dosage forms of pomalidomide having advantageous physical and pharmaceutical properties. Stability is mentioned among these properties (see paragraphs [0005] and [0025], and example 7). The solution proposed in claim 1 of the main request is a pharmaceutical dosage form comprising pomalidomide, mannitol and starch.

1.2 D1 is used as starting point by all parties and in the appealed decision.

D1 relates to a method of treating cutaneous lupus comprising administering one of four proposed 4-amino-isoindoline-derived active agents, including pomalidomide (see claims 1-4; pomalidomide corresponds to the active agent of claim 2, or to compound (2) of example 2, paragraph [0151]).

D1 also relates to dosage forms comprising one or more of these active agents (see §5.5 starting on page 10, right column; see claim 22, referring to any of claims 1-4). The description further provides lists of excipients that can be used in oral dosage forms, such as binders or fillers. Paragraph [0122] recites starches and pre-gelatinized starch among other binders. Paragraph [0124] lists starch, pre-gelatinized starch and mannitol among the fillers. Issues of stability in the presence of lactose or humidity are generally mentioned in paragraphs [0111] and [0113].

Examples 4-14 of D1 disclose pharmaceutical compositions comprising (generally) an active ingredient. Among these examples, the compositions of examples 4-7 comprise either mannitol (see example 6) or starch (see examples 4, 5, and 7) as excipient.

1.3 Differentiating features

D1 thus discloses, in one alternative of e.g. claim 22, pomalidomide dosage forms. The respondent suggested (see §3.24-3.25 of the reply) that a single selection may be acceptable for the purposes of assessing novelty but not for inventive step, such that no pomalidomide dosage form would be disclosed in D1. The Board does not concurs. The same definition of the prior art under Article 54(2) EPC and the same disclosure test apply in both cases. The Board emphasises that pomalidomide does

not simply notionally fall within the scope of D1, but is one of only four active ingredients recited and tested therein.

It is for the purposes of the present decision not necessary to establish whether, as submitted by the appellants, a more specific composition containing both pomalidomide and one of starch or mannitol forms part of the direct and unambiguous disclosure of D1. In any case, in the Board's view, the dosage forms of claim 1 of the main request represent a selection from the pomalidomide dosage forms generally disclosed in D1, i.e. the claimed formulation combines pomalidomide with two excipients which are also explicitly recited in D1, but not together in combination with pomalidomide. Starting from the pomalidomide composition of claim 22 of D1, the differentiating feature is the presence of both mannitol and starch.

1.4 Technical effect and problem

The respondent formulates the problem starting from D1 as the provision of a stable dosage form of pomalidomide that is suitable for clinical use. The appellants consider the problem to be the provision of an alternative pomalidomide oral dosage form.

1.4.1 The respondent stresses that their proposed objective technical problem relates to the provision of a stable dosage form of pomalidomide, not a more stable dosage form. According to the respondent, there are no prepared and tested pomalidomide formulations in D1 for carrying out a comparison, such that the respondent can rely on evidence supporting that the claimed invention provides a technical effect *per se*. In other words, the respondent considers that, since there are no stable

dosage forms shown in D1 which could serve as comparator, the achievement of a certain level of stability independently of any comparison with the prior art can be taken into account for the assessment of inventive step.

The Board does not agree. The circumstances of the case do not justify that the respondent be exonerated from their burden to properly demonstrate that the purported technical effect of the claimed invention have successfully been achieved in comparison with the prior art. Pomalidomide is one of only four active ingredients recited and tested in D1. The excipient selected in claim 1 do not simply fall notionally within the scope of D1 but are explicitly recited in the short list of fillers of paragraph [0124] and given emphasis by their use in the dosage forms of examples 4-7. Dosage forms of pomalidomide belong to the disclosure of D1, and the fact that this disclosure is generic in some respects does not mean that it is speculative or insufficient, nor allows the assumption that the formulations of D1 suffer from a lack of stability, especially considering that D1 addresses stability. The mere fact that D1 does not contain any prepared and tested specific formulations of pomalidomide does not change this conclusion, because, for the purposes of inventive step, the teaching of the prior art is not limited to prepared and tested examples.

An inventive step may be acknowledged to a selection if this selection is connected to a particular technical effect, and if no hints exist leading the skilled person to the selection. This however supposes that this particular technical effect be convincingly shown for the entire selected subset of formulations by a

meaningful comparison with other formulations falling within the ambit of D1.

1.4.2 The respondent cited several decisions to support their view that, when the prior art is unspecific, the achievement of a technical effect *per se* may be taken into account for the assessment of inventive step.

The Board firstly notes that in all the cited cases, experimental data were presented in respect of a differentiating feature (see T 1193/18, point 9.2 of the reasons regarding the effect of the claimed glycerol concentration range on stability; T 2342/19, point 3.3.5, technical effect linked with the claimed pH range; T 2200/17, point 9.5, comparison with the known prodrugs TD/TDF; T1126/19, point 6.4, effect of crystallinity and presence of forms A and/or B, and optionally C).

But more importantly, the Board does not agree with the respondent that D1 is unspecific, because, as explained above (see 1.4.1), the claimed active ingredient and two excipients are explicitly recited and part of a limited number of emphasised alternatives in D1.

1.4.3 It must accordingly be assessed whether the evidence on file convincingly demonstrates that the selection is associated with a technical effect over the pomalidomide formulations of D1, and whether this effect credibly arises over the whole claimed scope. The evidence cited in this respect is the application as filed, D4, and D31 / D31a.

1.4.4 The application as filed contains examples 1-6, showing pomalidomide dosage capsules containing both starch and mannitol. Example 7 describes a protocol for testing

both accelerated and long term stability. It is stated in paragraph [0139] that the "formulations provided herein" have adequate stability for clinical and other uses. However, even if it were accepted that the "formulations provided herein" refer to those of examples 1-6, it remains that no data, comparative or otherwise, are reported. The Board thus does not consider that the application as filed credibly demonstrates the technical effects of improved stability or improved suitability for clinical use for the claimed selected formulations in comparison with D1.

1.4.5 D4 compares the stability of several dosage forms (see page 3 of D4, formulations A-J as shown below):

Ingredient	Function	Formulation (Quantity per blend, %)									
		A	B	C	D	E	F	G	H	I	J
CC-4047 (Process B)	Active ingredient	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40	0.40
Anhydrous dibasic calcium phosphate	Bulking agent	45.35		95.35	45.35	45.35		45.35	45.35	45.35	
Spray dried mannitol	Bulking agent						45.35				
Pregelatinized starch	Bulking agent	50.00	95.35		54.00	50.25	50.00		50.00	50.00	
Starch (corn starch and pregelatinized)	Bulking agent							50.00			
Lactose anhydrous	Bulking agent										75.00
Microcrystalline cellulose	Bulking agent										20.60
Croscarmellose sodium	Disintegrant	4.00	4.00	4.00		4.00	4.00	4.00		4.00	4.00
Sodium starch glycolate	Disintegrant								4.00		
Sodium stearyl fumarate	Lubricant	0.25	0.25	0.25	0.25		0.25	0.25	0.25		
Magnesium stearate	Lubricant									0.25	1.00

Among the above formulations of D4, formulations A, C, E, G, H and I were found to present a compatibility problem i.e. to be unstable after two weeks storage. Formulations D, F, J did not present this compatibility issue. However, formulations D and J performed worse

than formulation F in a long term stability test. No results are reported for formulation B.

The most stable formulation F of D4 is according to claim 1 of the main request, and contains spray-dried mannitol (45.35%) and pregelatinized starch (50%) as sole bulking agents, together with croscarmellose sodium as disintegrant and sodium stearyl fumarate as lubricant. It differs from the other tested formulations of D4 not only by the presence of mannitol and starch in these specific grades, but also by the absence of other components, namely the anhydrous dibasic calcium phosphate of formulations A, C-E and G-I or the microcrystalline cellulose of formulation J.

1.4.6 In the Board's view, a comparison of (inventive) formulation F with any of the formulations A, C-E and G-I does not represent a proper comparison with D1, because the anhydrous dibasic calcium phosphate present in the comparative formulations A, C-E and G-I is nowhere mentioned in D1. A fair comparison with D1 should take account of the guidance given therein and the emphasis on a few explicitly recited excipients/ fillers, in the examples and in paragraph [0124], which reads:

> "Non-limiting examples of fillers suitable for use in the pharmaceutical compositions and dosage forms disclosed herein include talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch and mixtures thereof."

Accordingly, a comparison with D1 cannot be made with compositions comprising an excipient (here, dibasic calcium phosphate) which, although notionally falling

within the scope of the broadest disclosure of D1 (see e.g. paragraph [0111]), is nowhere explicitly mentioned in D1. As expressed by appellant O1, the effect must be shown over what is disclosed in D1, and not over what is not excluded by it. Accordingly, formulations A, C-E and G-I are not proper comparative formulations representative of D1.

1.4.7 As to a comparison with formulation J, it is not credible that the observed improved stability of formulation F originates from the differentiating feature (the presence of mannitol and starch), or arises over the scope of claim 1. Instead, this observed effect can be linked to other features which are not part of claim 1, namely the absence of water or of the water-containing microcrystalline cellulose of formulation J (as explained in D4 itself, §12), and the use, in formulation F, of low moisture grade excipients (spray-dried mannitol, pregelatinized starch), considering the known detrimental effect of moisture (see D1, paragraphs [0111] and [0112]).

The respondent counters in particular that the excipients used in formulations A-J of D4 were all found to be compatible in 1:1 compatibility tests (see §6 of D4). The Board does not find this argument convincing. These compatibility tests are merely summarised in D4 without any information as to their setup (e.g. the amounts of excipient and pomalidomide or the temperature and humidity used). There is in this regard no indication that the broadly defined conditions mentioned in D16 (see page 352, 4th paragraph) were followed. The only information in D4 about these tests is that "1:1 compatibility tests have been conducted between pomalidomide and various candidate excipients" which are then recited, and that

"From the testing, it was found that pomalidomide is compatible with each of those excipients tested". Thus no conclusion can be drawn from these compatiblity tests. In particular, the absence of observed compatibility issue with microcrystalline cellulose (MCC) under these undisclosed test conditions does not make it credible that the stability issue with the MCC-containing formulation J are not due to MCC, especially in view of the explicit statement in D4 that "the stability issue observed in that formulation was attributed to the presence of microcrystalline cellulose" (see §12).

Consequently, D4 does not show that the improved stability of formulation F in comparison with formulation J find its origin in the differentiating feature over D1 (the selection of mannitol and starch), rather than other non-claimed features.

1.4.8 D31 and D31a were filed by appellant O1 during appeal proceedings. The respondent contested their admittance into the proceedings. The Board decided at the oral proceedings to admit D31 and D31a. Considering that D31 and D31a are not relied on in the present decision to conclude to lack of inventive step, it is not necessary to detail the reasons for their admittance.

Nonetheless, the respondent briefly relied on D31 and D31a as confirmation of the stability *per se* of the claimed compositions. For the sake of completeness, the Board notes not only that this argument contradicts the respondent's earlier argument that D31 and D31a have no probative value, but also that, in any case, D31 and D31a do not show any improvement of the claimed formulations in comparison with those of D1. Hence, D31 and D31a do not change the Board's conclusion.

1.4.9 The respondent further emphasised that the claimed formulations are not only stable but also suitable for clinical use. This suitability is understood by the respondent as implying further advantageous properties such as flowability or ability to be batch processed into capsules. However, no such advantage is shown to arise as a result of the differentiating features, whether in the examples in the application as filed or formulation F in D4. The mere fact that the Imnovid® product is marketed cannot make up for the absence of such comparative evidence. Hence these advantages cannot be taken into account in the formulation of the technical problem.

1.5 The problem to be solved is thus seen in the provision of an alternative pomalidomide oral dosage form.

Since the claimed selection is not shown to be associated with any technical effect, this selection is arbitrary and does not involve an inventive step. Considering that the problem is only formulated as the provision of an alternative, the lack of preference expressed in D1 for the features selected in present claim 1 (namely pomalidomide, oral dosage forms, or the excipients of paragraph [0124]) does not establish an inventive step, because the chosen alternative is not shown to be any more suitable than the others considered in D1.

The respondent argues that no example of pomalidomide formulation are actually given in D1, that a specific research project is required to arrive at formulations of each API taking into account its chemical or physical properties (see D16, pages 347, 348, 352 and 369), and that developing a stable formulation of

pomalidomide presents particular challenges as shown in D4.

The Board considers that the general statements in D16, emphasising the difficulties in formulating APIs in general, are not relevant in the present case where the disclosure D1 is sufficiently specific. As explained above (see 1.4.1), pomalidomide is one of only four related active ingredients shown in D1, and the two claimed excipients are explicitly recited in a list of fillers "suitable for use in the pharmaceutical compositions and dosage forms disclosed herein" (see D1, paragraph [0124]). There is no demonstration that the skilled person, starting from D1 and taking into account its guidance on the formulation of the active ingredients considered therein, would encounter any difficulty in formulating pomalidomide. D4 does not prove that such a difficulty would arise when starting from D1, because the trial formulations exhibiting instability in D4 contain ingredients (anhydrous dibasic calcium phosphate or moisture-containing MCC, see 1.4.6 and 1.4.7 above) which are not mentioned in D1 or would be anticipated to be unsuitable considering its teaching (see the statement regarding exposure to water in paragraph [0111]).

According to the respondent, lactose is alternatively described in D1 as detrimental (see paragraph [0111]-[0112]) or as part of the composition in examples 4-7. However, the presence of lactose if neither specified nor excluded by present claim 1, such that this argument does not modify the conclusion.

Accordingly, the subject-matter of the main request does not involve an inventive step.

2. Auxiliary requests

The amendments carried out in claim 1 of auxiliary requests 1-41 are:
- the limitation to oral pharmaceutical dosage forms, or to oral dosage unit form selected from tablets, caplets, and capsules, and/or
- the addition of the feature that the mannitol and starch comprise 70-99 wt%, 90-99 wt% or 95-99 wt% of total weight of the pharmaceutical dosage form, and/or
- the limitation to a mannitol : starch ratio of from 1:1 to 1:1.5.

None of these modifications change the finding of lack of inventive step. In all cases, the claimed formulation constitutes a selection from the teaching of D1 which is not shown to be associated with any effect.

Accordingly, the same conclusion applies. None of the auxiliary requests meets the requirements of inventive step.

Order

For these reasons it is decided that:

The decision under appeal is set aside.

The patent is revoked.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated