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Datasheet for the decision of 3 June 2025

Case Number: T 0469/23 - 3.3.07

Application Number: 13182721.4

Publication Number: 2695609

IPC: A61K9/20, A61K9/28, A61K31/7068

Language of the proceedings: EN

Title of invention:
Oral formulations of cytidine analogs and methods of use thereof

Patent Proprietor:
Celgene Corporation

Opponents:
Generics (U.K.) Limited
Teva Pharmaceutical Industries Ltd.
Hoffmann Eitle
Sandoz AG

Headword:
Oral azacytidine II/CELGENE

Relevant legal provisions:
EPC Art. 76(1), 123(2), 84
RPBA 2020 Art. 12(6)
Guidelines for examination F-IV 4.7

Keyword:
Amendments - added subject-matter (yes)
Claims - clarity - auxiliary request (no)
Late-filed request - should have been submitted in first-instance proceedings (yes)

Decisions cited:
T 1269/06, T 0992/22, T 0145/22, T 3035/19, G 0003/14

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Boards of Appeal

Chambres de recours

Boards of Appeal of the
European Patent Office
Richard-Reitzner-Allee 8
85540 Haar
GERMANY
Tel. +49 (0)89 2399-0

Case Number: T 0469/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 3 June 2025

Appellant: (Patent Proprietor)	Celgene Corporation Route 206 & Province Line Road Princeton, NJ 08543 (US)
Representative:	Carpmaels & Ransford LLP One Southampton Row London WC1B 5HA (GB)
Respondent: (Opponent 1)	Generics (U.K.) Limited Building 4, Trident Place Mosquito Way Hatfield Herts AL10 9UL (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Opponent 2)	Teva Pharmaceutical Industries Ltd. 124 Dvora HaNevi'a St. 6944020 Tel Aviv (IL)
Representative:	D Young & Co LLP 3 Noble Street London EC2V 7BQ (GB)
Respondent: (Opponent 3)	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastrasse 30 81925 München (DE)
Representative:	Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)

Respondent: (Opponent 4)	Sandoz AG Centralbahnstrasse 4 4051 Basel (CH)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 2 January 2023 revoking European patent No. 2695609 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 2 695 609 ("the patent") was granted based of fourteen claims. It derived from a divisional application with respect to the earlier European patent application 09746975.3 originally published as PCT application WO 2009/139888 A1.

Claim 1 as granted defined:

"A pharmaceutical composition for use in a method of treating a subject having cancer, wherein said method comprises orally administering said pharmaceutical composition once per day, and wherein said pharmaceutical composition comprises a therapeutically effective amount of 5-azacytidine and is an immediate release composition."

Dependent claim 2 as granted further defined the additional feature:

"wherein said method comprises administering daily to the subject said pharmaceutical composition for 7 or more days".

II. Four oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked novelty and inventive step, that the claimed invention was not sufficiently disclosed and that the patent comprised subject-matter extending beyond the content of the (earlier) application as filed.

The patent proprietor filed the appeal against the decision of the opposition division to revoke the patent.

The decision was based on the patent as granted (main request), auxiliary requests 1-5 filed on 8 April 2021 and auxiliary requests 6-23 filed on 15 September 2022.

Claim 1 of auxiliary request 1 additionally defined with respect to claim 1 of the main request that the composition releases the 5-azacytidine substantially in the stomach following oral administration to the subject.

Claim 1 of auxiliary request 2 additionally defined with respect to claim 1 of the main request that the composition releases the 5-azacytidine in the stomach following oral administration to the subject.

Claim 1 of auxiliary request 3 additionally defined with respect to claim 1 of the main request that the cancer is myelodyplastic syndrome (MDL) or acute myelogenous leukemia (AML).

Claim 1 of auxiliary request 4 includes the amendments to claim 1 of the main request as introduced in auxiliary requests 1 and 3.

Claim 1 of auxiliary request 5 includes the amendments to claim 1 of the main request as introduced in auxiliary requests 2 and 3.

Auxiliary requests 6-11 correspond respectively to the main request and auxiliary requests 1-5 in which claim 1 additionally defines that the use concerns a method of treating cancer in a subject having cancer.

Auxiliary requests 12-23 correspond respectively to the main request and auxiliary requests 1-11 in which claim 2 is deleted.

The opposition division cited *inter alia* the following documents:

D9: Leukemia, 2008, 22, 1680-1684
D15: Applied Biopharmaceutics & Pharmacokinetics, 5th edition, 2005, 515
D16: ICH Topic Q 6 A: Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, European Medicines Agency, May 2000
D17: Aulton's Pharmaceutics: The Design and Manufacture of Medicines, 3rd edition, 2007, 454-455
D55: Clinical Pharmacokinetics Concepts and Applications, 3rd edition, 1995, 11-12, 128-129 and 131-132.

The opposition division arrived at the following conclusions:

(a) The patent as granted comprised subject-matter extending beyond the original disclosure, because the application as originally filed disclosed the immediate release as defined in claim 1 as granted only in the context of a composition which released the 5-azacytidine substantially in the stomach following oral administration. Moreover, the definition of an immediate release composition without the limitation of the release substantially in the stomach and the definition of the once daily administration represented an impermissible dual selection with respect to the original disclosure. The combination of the once per day administration

with the duration of treatment for 7 days as defined in claim 2 as granted involved an additional selection which could not be directly and unambiguously derived from the original disclosure.

(b) The claims of auxiliary requests 1-12 comprised subject-matter which did not comply with Articles 76(1) and 123(2) EPC for similar reasons as presented with respect to the main request.

(c) Auxiliary request 13 did not comply with Article 84 EPC, because the expression "substantially in the stomach" lacked clarity.

(d) The feature of the treatment involving the administration of the pharmaceutical composition once per day defined in claim 1 of auxiliary request 14 included the administration of only a single dosage. The claimed subject-matter lacked novelty in view of document D9, which already described the effective oral administration of a single dosage of the defined pharmaceutical composition to cancer patients.

(e) Auxiliary requests 15, 18 and 21 did not comply with Articles 76(1) and 123(2) EPC for similar reasons as presented with respect to the main request.

(f) Auxiliary requests 16, 19 and 22 did not comply with Article 84 EPC for similar reasons as auxiliary request 13.

(g) Auxiliary requests 17, 20 and 23 did not comply with the requirement of novelty for similar reasons as auxiliary request 14.

III. With the statement of grounds of appeal, the patent proprietor maintained the main request and filed auxiliary requests 1-47, whereby auxiliary requests 1-23 corresponded to the auxiliary requests 1-23 on which the decision under appeal was based.

Auxiliary requests 24-47 corresponded respectively to the main request and auxiliary requests 1-23 in which claim 1 additionally defines the feature:

"using a treatment cycle comprising administration of 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg, or 1,000 mg of 5-azacytidine once per day for 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 days,"

IV. In its communication pursuant to Article 15(1) RPBA the Board questioned whether the subject-matter of claims 1 and 2 as granted could be directly and unambiguously derived from the original disclosure, because these claims seemed to define the combination of a plurality of selected features with respect to the original disclosure, including the selection an immediate release composition and the once per day oral administration in claim 1 and the further definition of the administration for 7 or more days in claim 2.

The Board expressed its doubts whether the auxiliary requests introducing the feature "substantially in the stomach" in the claims complied with the requirement of clarity and questioned whether the original disclosure provided a suitable basis for the introduction of the

feature concerning the release in the stomach without the term "substantially".

The Board further indicated that it intended not to admit the new auxiliary requests 24-47 into the appeal proceedings.

V. Oral proceedings were held on 3 June 2025. During the oral proceedings the patent proprietor withdrew auxiliary requests 13 and 14.

VI. The arguments of the patent proprietor relevant to the present decision are summarized as follows:

Claim 1 as granted involved with respect to the content of the PCT application as originally filed the permissible selection of the disclosed frequency of once per day oral administration.

The claims of the application as originally filed explicitly defined a pharmaceutical composition in the form of an orally administered immediate release composition as a distinct embodiment of the claimed invention. The application as originally filed further specifically described that the disclosed formulations may generally be provided in the form of immediate release compositions for oral administration without the explicit requirement of the release of the active agent substantially in the stomach. In view of the common general knowledge the release of the 5-azacytidine substantially in the stomach would anyway be implied in case of the defined oral administration of the immediate release compositions. The defined immediate release compositions did not comprise the type of orally disintegrating tablets for

absorption through the oral mucosa which was disclosed in the patent as a distinct category of compositions.

Applying the principles as established in the jurisprudence, in particular T 1269/06 and T 992/22, claim 1 as granted did not comprise subject-matter extending beyond the original disclosure, because no new technical information resulted from the combination of the generally disclosed embodiment of the pharmaceutical composition being in the form of an immediate release composition with the selected feature of the oral administration once per day. Example 4 of the original disclosure provided furthermore a specific pointer towards this combination.

The feature concerning the daily administration for 7 or more days as defined in dependent claim 2 as granted was disclosed in the original application as the broadest embodiment in a list of explicitly described durations of administration. The definition of this feature in claim 2 as granted did therefore not involve any specific additional selection with respect to the content of the originally filed application.

In line with the Board's findings in T 145/22 concerning the patent granted for the parent application, claim 1 of auxiliary request 15 was directly and unambiguously derivable from the embodiment concerning the utility of 5-azacytidine in an immediate release composition for oral administration for treatment of MDL or AML as explicitly claimed in the application as originally filed in combination with the described once per

day administration. Example 4 of the original disclosure provided a specific pointer towards this combination.

The feature of the release of the 5-azacytidine substantially in the stomach, as in claim 1 of auxiliary request 16, was in accordance with the considerations in G 3/14 not open to an objection of lack of clarity, because it did not introduce any ambiguity regarding the amount of 5-azacytidine released in the stomach from an oral immediate release composition as defined in claim 1 as granted.

In line with the Case Law of the Boards of Appeal of the EPO, 10th edition, 2022, Section II.A.3.6, the meaning of a relative term such as "substantially" was to be understood in the given context. Apart from the guidance in the patent regarding the meaning of the expression "substantially in the stomach" *per se*, the introduced feature was clear in the context of an orally administered immediate release composition, because the person skilled in the art would understand that oral administration of an immediate release composition results in the release of the active agent substantially in the stomach. The introduction of the feature was anyway of no relevance to the contribution of the claimed invention over the prior art.

In line with the Guidelines for Examination in the EPO, F-IV 4.7, the skilled person would furthermore understand that in the context of an immediate release composition for oral administration the definition of the release of the 5-azacytidine in

the stomach in which the term "substantially" is omitted, as in claim 1 of auxiliary request 17, did not result in a change of the technical information with respect to the content of the original application.

Auxiliary requests 24-47 introduced a single amendment to the preceding requests which was responsive to the finding in the decision under appeal that the feature "once per day" did not require administration on more than one day and was therefore anticipated by the administration of a single dose described in the prior art. These requests should be admitted under Article 12(4) RPBA, because they were timely filed with the statement of grounds of appeal and clearly resolved the identified issue without introducing new issues that would be contrary to the purpose of orderly and efficient proceedings. The admittance of these requests was furthermore not contrary to Article 12(6) RPBA, which according to the Case Law of the Boards of Appeal of the EPO, 10th edition, 2022, Section V-A 4.3.1, seeks to avoid compelling the Board either to give a first ruling on critical issues or to remit the case to the department of first instance, which would run counter to orderly and efficient proceedings.

VII. The arguments of the opponents relevant to the present decision are summarised as follows:

The definition of the subject-matter in claim 1 as granted involved the combination of multiple features selected from the original disclosure, in particular the feature of the oral administration once per day and the feature of an immediate

release composition independent of the release of the 5-azacytidine substantially in the stomach.

The claims of the original application did not provide a basis for the selection of the immediate release compositions in general, because they specifically related to formulations which released of the 5-azacytidine substantially in the stomach. Taking account of the explanations in the patent and the common general knowledge, the feature of delivery substantially in the stomach was not implicit in the definition of an orally administered composition for immediate release in claim 1 as granted.

The original application did not present a pointer to the combination of the feature of the oral administration once per day and the feature of an immediate release composition. The patent proprietor's argument relying on examples in the original disclosure as relevant pointer should not be admitted, because it was presented for the first time during the oral proceedings. This argument was anyway not convincing, because example 5 referred to single as well as multiple dosing and because example 4 related specifically to compositions for release substantially in the stomach and did not unambiguously relate to treatment by once per day administration. In line with the established jurisprudence as referred to in T 3035/19, the specific combination of the selected features represented new technical information that could not be directly and unambiguously derived from the original disclosure in the absence of such a pointer.

The definition of the daily administration for 7 or more days in dependent claim 2 involved the additional selection of the minimal duration of the treatment from a list of originally disclosed possibilities thereof. The combination of this selected feature with the feature of the administration once per day was not directly and unambiguously derivable from the original disclosure.

Claim 1 of auxiliary request 15 involved the same impermissible combination of the feature of the administration once per day with the feature of the immediate release composition as claim 1 as granted.

The patent proprietor's argument, that the feature of the release of the 5-azacytidine substantially in the stomach, as introduced in claim 1 of auxiliary request 16, was in view of the considerations in G 3/14 not objectionable for lack of clarity, should not be admitted, because it was presented for the first time during the oral proceedings. This argument was anyway not convincing, because the introduction of this feature resulted in a lack of clarity due to the ambiguous term "substantially", which also in the context of the defined compositions did not have a generally recognized meaning and which related according to the description to a variety of different meanings.

The feature of the release of the 5-azacytidine in the stomach as introduced in claim 1 of auxiliary request 17 involved subject-matter extending beyond the content of the original application due to the

omission of the term "substantially" from the expression as used in the original disclosure. This omission resulted in a different technical teaching.

Auxiliary requests 24-47 were not justified as a response to the decision under appeal and should have been filed during the first instance proceedings following the preliminary opinion expressed by the opposition division. Moreover, the amendment to the claims according to these requests incorporated features only disclosed in the description of the application which raised additional and complex issues to be dealt with for the first time during the appeal proceedings.

VIII. The appellant-patent proprietor requested that the decision under appeal be set aside, and the patent be maintained as granted (main request). As an auxiliary measure the patent proprietor requested that the patent be maintained based on one of auxiliary requests 1-12 and 15-47 as filed with the statement setting out the grounds of appeal.

IX. The respondents-opponents requested that the appeal be dismissed. They furthermore requested that auxiliary requests 24-47 not be admitted into the appeal proceedings.

Reasons for the Decision

1. Main request - added subject-matter

1.1 It was common ground that the technical content of the divisional application as originally filed from which

the patent derives corresponds to the content of the earlier application as published in WO 2009/139888 A1.

The Board therefore refers to this content as published in WO 2009/139888 A1 for the assessment of the requirement that amendments may not result in subject-matter extending beyond the content of the original application as formulated in Articles 76(1) and 123(2) EPC, and as reflected in the ground of opposition under Article 100(c) EPC.

1.2 Claim 1 as granted

1.2.1 Claim 1 as granted defines the combination of the feature of the pharmaceutical composition being an immediate release composition and the feature of its oral administration once per day.

1.2.2 It was not in dispute that the feature of the once per day oral administration was selected from a list of possibilities including oral administration once per day, twice per day, three times per day, four times per day, or more than four times per day as disclosed in paragraph [00175] of the original application.

1.2.3 Claims 33 and 71 of the original application specifically relate to the utility of a pharmaceutical composition comprising 5-azacytidine in the treatment of a disease associated with abnormal cell proliferation wherein the composition releases the 5-azacytidine substantially in the stomach following oral administration. The original claims 41 and 74 depending thereon further define the composition as an immediate release composition. Moreover, the original dependent claims 34-39 and 72 define certain specific forms of cancer as the disease to be treated.

In line with the definition of the subject-matter in the original claims, the application as filed describes in paragraph [0015] under the heading "Summary" that pharmaceutical compositions comprising cytidine analogs such as 5-azacytidine are provided, wherein the compositions release the active pharmaceutical ingredient (API) substantially in the stomach upon oral administration. However, the application as filed also describes from paragraph [00108] onwards under the heading "C. Pharmaceutical Formulations" embodiments relating to pharmaceutical formulations comprising a cytidine analog such as 5-azacytidine which are prepared for oral administration, and which are described to be only preferably for release substantially in the stomach. In paragraph [00110] under the sub-heading "Performance of Certain Dosage Forms Provided Herein" the application as filed specifically describes that in certain embodiments the formulations comprising a cytidine analogue such as 5-azacytidine are orally administered compositions for immediate release without specific reference to the release in the stomach. In contrast, the original application describes in the subsequent paragraph [00111] certain alternative embodiments in which the formulations effect a controlled release of the API substantially in the stomach. Subsequently, the application as filed (see e.g. paragraphs [00114] and [00122]) repeatedly refers to immediate release oral formulations **and/or** formulations that release the active agent substantially in the stomach. In paragraph [00137] the application as filed further describes that in certain embodiments the composition may be a sublingual tablet for absorption through the oral mucosa, which may dissolve promptly and provide rapid release of the drug.

From paragraphs [00108], [00110] and [00137] it is evident that the original disclosure as a whole expressly includes orally administered immediate release compositions comprising 5-azacytidine without the requirement regarding the release in the stomach as a distinct embodiment. Contrary to the finding in the decision under appeal, the original disclosure is thus not restricted to the originally claimed compositions which require the release of the active agent substantially in the stomach.

However, in view of the alternative embodiments described in paragraph [00111] relating to formulations which effect a controlled release of the API substantially in the stomach, it is also evident that the choice defined in claim 1 as granted for the alternative embodiment of an oral immediate release composition without the requirement of the release substantially in the stomach implies a further selection with respect to content of the original disclosure.

1.2.4 According to the Board, the skilled person understands that the release substantially in the stomach as required according to the original claims is not an inherent feature of the orally administered immediate release composition as defined in claim 1 as granted. This follows from the designation of a sublingual tablet as a specific form of an immediate release composition in document D17, which undisputedly represents common general knowledge (see D17, page 454, under "TABLET TYPES"). The separate mention of the administration by the oral route and the administration by the sublingual or buccal routes in document D55 (see D55, page 11, under "Sites of Administration") relied

upon by the patent proprietor does not exclude sublingual and buccal tablets from the general category of orally administered formulations. Documents D15 and D16, which were also relied upon by the patent proprietor, merely indicate that most conventional oral drug products, such as tablets and capsules, release the active drug immediately after oral administration (see D15, page 515, lines 1-5) and that immediate release allows the drug to dissolve in the gastrointestinal contents with no intention of delaying or prolonging the dissolution or absorption (see D16, page 19). Documents D15 and D16 do thereby not disqualify rapidly disintegrating tablets intended to dissolve in the mouth after oral administration as orally administered immediate release compositions. Notably, this understanding is in line with the content of the application as filed, which relates to orally administered formulations and mentions rapidly disintegrating tablets that dissolve in the mouth and sublingual tablets as specific embodiments thereof (see paragraphs [0108]-[0109], [0123] and [0137]-[0138]). The choice of an oral immediate release composition defined in claim 1 as granted without the requirement of the release substantially in the stomach does therefore not follow from any preference for immediate release compositions which release the 5-azacytidine substantially in the stomach expressed in the claims of the original application.

1.2.5 According to T 1269/06 (reasons 2) it should in case of an impermissible amendment be possible to identify clearly the technical information which has been added with respect to the original disclosure. In T 992/22 (reasons 2.4.3) it was held that the decisive question is not if and how many selections have been made, but whether the amendments add information that is not

directly and unambiguously derivable from the original application.

It is established jurisprudence (see Case Law of the Boards of Appeal of the EPO, 10th edition, 2022, Section E.II.1.6.2; see in particular T 3035/19, reasons 1.2-1.6) that such added technical information may be identified in the unsupported combination of features selected from independent lists or pertaining to separate embodiments disclosed in the original disclosure, in particular where the application as originally filed does not provide any clear pointer to such a combination.

The Board further notes that the issue to be decided in T 992/22 concerned amendments in the definition of compounds by a Markush formula which involved restrictions in lists of variables which did not result in a specific combination of substituents (see T 992/22, see section 2.4.4). In contrast, the present case involves the specific combination of the feature of the pharmaceutical composition being an immediate release composition and the feature of its oral administration once per day.

1.2.6 The Board does not recognize that in the present case the original disclosure provides any pointer to the combination of the feature of the pharmaceutical composition being an immediate release composition (in general and thus without the feature of the release substantially in the stomach) with the feature of its oral administration once per day as defined in claim 1 as granted.

During the oral proceedings the patent proprietor relied on Example 4 of the original application as

providing a relevant pointer. The argument was most extensively developed in the context of auxiliary request 15, but applies equally to the main request. Example 4 of the original disclosure describes a multiple dose escalation study in which patients with MDS or AML were treated in a first cycle with subcutaneous doses of azacytidine and in subsequent cycles with orally administered azacytidine with "dosing on Day 1-7 for each cycle" (see paragraph [00217]). Pharmacokinetic (PK) plasma profiles of azacytidine following the oral administration on days 1 and 7 are reported in Figure 3, which presents curves spanning a frame of 8 hours with a single maximum after about 1-1.5 hours. These results in Figure 3 seem to indicate the once per day administration, at least on day 1 and 7, from which the plasma PK profiles are presented. However, Example 4 does not provide any express statement regarding the once per day frequency of administration on day 1 and 7, let alone any statement regarding once per day administration during the whole cycle of treatment. At the same time, it is expressly concluded in Example 4 that the data demonstrate patient improvement following administration of azacytidine formulated for release substantially in the stomach (see paragraph [00225]). The Board therefore concludes that with Example 4 the original disclosure does not provide a clear pointer to the combination of the immediate release composition and the once per day administration features as defined in claim 1 as granted. This conclusion finds confirmation in the express statement in Example 5 of the original application that the PK data from a separate clinical study involving the oral administration of azacytidine support not only its single but also multiple daily dosing.

In view of this conclusion the opponents' objection to the admittance of the patent proprietor's argument relying on Example 4 does not need to be addressed.

1.2.7 Accordingly, the Board concludes that claim 1 as granted comprises subject-matter extending beyond the content of the application and the earlier application as filed.

1.3 Claim 2 as granted

1.3.1 Claim 2 as granted is dependent on granted claim 1 and defines the additional feature of daily administration of the pharmaceutical composition for 7 or more days.

Accordingly, claim 2 defines the combination of the feature regarding the duration of the daily administration with the features of once per day oral administration and an immediate release composition.

1.3.2 The original application presents in paragraph [00176] the following disclosure which the patent proprietor relied upon as basis for claim 2 as granted:

"For example, in certain embodiments, methods provided herein comprise administering daily to a subject an oral formulation provided herein for 7 or more, 8 or more, 9 or more, 10 or more, 11 or more, 12 or more, 13 or more, 14 or more, 15 or more, 16 or more, 17 or more, 18 or more, 19 or more, 20 or more, or 21 or more days."

It is evident that additional feature defined in claim 2 corresponds to the broadest specific range for the duration of daily administration and thus comprises all the other specific ranges disclosed in paragraph

[00176]. The patent proprietor argued that the additionally feature defined in claim 2 does therefore not imply any selection and that accordingly the combination of this feature with the features of claim 1 does not present the skilled person with any new information.

However, the Board observes that the definition in claim 2 of the broadest range for the duration of the oral administration of the 5-azacytidine presented in paragraph [00176] corresponds to the technically relevant selection of a specific minimum for the duration of the administration from a list of alternatives for the minimum duration described in the original application. Claim 2 therefore defines the specific combination of this selected feature of the minimum for the duration of administration with each of the selected features of claim 1 identified in section 1.2 above.

No pointer towards this specific combination of selected features in the original disclosure was identified. As pointed out in section 1.2.5 above, it is established jurisprudence that added technical information may be identified in the unsupported combination of selected features, in particular in the absence of a pointer to such selection.

1.3.3 Accordingly, the Board concludes that claim 2 as granted comprises subject-matter extending beyond the content of the application and the earlier application as filed.

2. Auxiliary requests

2.1 Overview of the amendments

The amendments according to the maintained auxiliary requests 1-12 and 15-47 with respect to the main request as identified in sections II and III above are schematically represented in the following table:

Auxiliary request	Substantially in stomach	~~Substantially~~ in stomach	Cancer is MDS/AML	Treating cancer	Deletion claim 2	200-1000mg 7-30 days
1	x					
2		x				
3			x			
4	x		x			
5		x	x			
6				x		
7	x			x		
8		x		x		
9			x	x		
10	x		x	x		
11		x	x	x		
12					x	
~~13~~	x				x	
~~14~~		x			x	
15			x		x	
16	x		x		x	
17		x	x		x	
18				x	x	
19	x			x	x	
20		x		x	x	
21			x	x	x	
22	x		x	x	x	
23		x	x	x	x	
24-47						x

2.2 Auxiliary requests 1-12

Auxiliary requests 1-11 include in claim 2 the definition of the combination of the feature of the once per day oral administration and the feature of the daily administration for 7 or more days. As explained in relation to the main request in section 1.3 above, the Board considers that this combination cannot be directly and unambiguously derived from the original disclosure.

Auxiliary request 12 includes the unamended claim 1 of the main request. As explained in relation to the main request in section 1.2 above, the Board considers that the subject-matter therein defined cannot be directly and unambiguously derived from the original disclosure.

The Board therefore concludes that auxiliary requests 1-12 do not comply with Articles 76(1) and 123(2) EPC.

2.3 Auxiliary requests 15, 18 and 21

Auxiliary requests 15, 18 and 21 include in claim 1 the definition of the same combination of the feature of the once per day oral administration and the feature of the immediate release composition as defined in claim 1 as granted.

As explained in relation to the main request in section 1.2 above, the Board considers that this combination cannot be directly and unambiguously derived from the original disclosure.

The Board observes that the more specific definition of MDL and AML as the cancer to be treated aligns the therapeutic indication defined in claim 1 of auxiliary requests 15 and 21 with the specific types of cancer of the patients in the study of Example 4 and explicitly defined in claim 72 of the original application. However, this amendment concerning the therapeutic indication does not affect the Board's findings, as for claim 1 as granted, that the claims of the application as originally filed do not support the definition of the orally administered immediate release compositions comprising 5-azacytidine without the requirement regarding the release in the stomach as a distinct

embodiment, and that Example 4 of the original disclosure does not provide a pointer to the combination of the feature of the once per day oral administration and the feature of the immediate release composition.

The Board further observes that in T 145/22, which concerned the patent granted for the parent application, it was concluded that the original disclosure expressly included orally administered immediate release compositions comprising 5-azacytidine without the requirement of the release in the stomach as an alternative embodiment which was permissibly combined with the embodiment of treatment of AML that had been highlighted in the original disclosure (see T 145/22, reasons 2). The findings regarding permissible amendments in T 145/22 do thus not concern the issue in the present case regarding the combination of the feature of the immediate release composition with the feature of the once per day oral administration.

The Board therefore concludes that auxiliary requests 15, 18 and 21 do not comply with Articles 76(1) and 123(2) EPC.

2.4 Auxiliary requests 16, 19 and 22

2.4.1 Auxiliary requests 16, 19 and 22 introduce in claim 1 with respect to claim 1 as granted the feature that the composition releases the 5-azacytidine substantially in the stomach following oral administration to the subject.

2.4.2 The patent defines in paragraph [00045] the meaning of the expression "substantially in the stomach" as follows:

"The term "substantially in the stomach," when used herein in reference to a composition, formulation, or dosage form provided herein, means that at least about 99%, at least about 95%, at least about 90%, at least about 85%, at least about 80%, at least about 75%, at least about 70%, at least about 65%, at least about 60%, at least about 55%, at least about 50%, at least about 45%, at least about 40%, at least about 35%, at least about 30%, at least about 25%, at least about 20%, at least about 15%, or at. [sic] least about 10% of the cytidine analog is released in the stomach."

In the context of the intended pharmaceutical compositions releasing the 5-azacytidine substantially in the stomach the patent itself thereby acknowledges the ambiguity of the term "substantially" by providing a variety of alternative meanings ranging from at least 10% to at least 99%.

Due to the ambiguous nature of the term "substantially" the amendment defining the feature of the release "substantially in the stomach" introduces ambiguity in claim 1 of auxiliary requests 16, 19 and 22, because it requires some substantial amount to be released in the stomach but does not provide the skilled person with clear criteria to determine when an amount is to be considered substantial.

2.4.3 The patent proprietor argued that claim 1 in auxiliary requests 16, 19 and 22 was clear, because the features of the claim were to be understood in the given context and the skilled person would be well aware that oral

administration of an immediate release composition results in the release of the active agent in the stomach. Moreover, the introduction of the feature was anyway of no relevance to the contribution of the claimed invention over the prior art.

However, as explained in sections 1.2.3 and 1.2.4 above, the definition of an orally administered immediate release composition does not by itself imply the release of the 5-cytidine substantially in the stomach. The proprietor's argument does therefore not resolve the identified ambiguity resulting from the lack of clear criteria for determining when according to the amended claim 1 in auxiliary requests 16, 19 and 22 the release of the 5-cytidine is substantial. This ambiguity results from the amendment independently of the question of the claimed contribution over the prior art.

2.4.4 The patent proprietor further argued that the amendment in claim 1 in auxiliary requests 16, 19 and 22 could not be considered to introduce ambiguity regarding the amount of 5-azacytidine released in the stomach, because the amount released in the stomach was determined by the form of the oral immediate release composition as already defined in claim 1 as granted. The patent proprietor contended that the claim 1 as amended in these requests was therefore not open to an objection of lack of clarity in view of G 3/14.

However, the Board observes that claim 1 as granted does not define any requirement as to the amount of 5-azacytidine released in the stomach, whereas the amendment in claim 1 of auxiliary requests 16, 19 and 22 introduces such a requirement without allowing the skilled person to determine when or not this

requirement is fulfilled. The patent proprietor's argument that the amendment does not introduce any ambiguity with respect to the claims as granted is therefore not considered convincing.

In view of this conclusion the opponents' objection to the admittance of the patent proprietor's argument referring to G 3/14 does not need to be addressed.

2.4.5 Accordingly, the Board has decided that auxiliary requests 16, 19 and 22 cannot be allowed, because they do not comply with Article 84 EPC.

2.5 Auxiliary requests 17, 20 and 23

2.5.1 Auxiliary requests 17, 20 and 23 include in claim 1 the amendment with respect to claim 1 as granted that the composition releases the 5-azacytidine in the stomach following oral administration to the subject without the term "substantially".

2.5.2 As explained in sections 1.2.3 and 1.2.4 above, the definition of an orally administered immediate release composition does not by itself imply the release of the 5-cytidine in the stomach, but the originally filed application does specifically disclose orally administered immediate release compositions which release the 5-azacytidine substantially in the stomach.

The application as originally filed presents in paragraph [00066] the same variety of alternative meanings for the expression "substantially in the stomach" as mentioned in section 2.4.2 above ranging from at least 10% to at least 99%. The original application does therefore not disclose orally administered immediate release compositions which

release substantially all 5-azacytidine in the stomach, but rather compositions which release at least a certain amount of the 5-cytidine depending on the chosen alternative meaning of the expression "substantially in the stomach".

Due to the omission of the term "substantially", claim 1 of auxiliary requests 17, 20 and 23 may be understood to either require that the 5-azacytidine is entirely released in the stomach or that at least some unspecified amount of 5-azacytidine is released in the stomach. The application as originally filed neither disclosed that the 5-azacytidine is entirely released in the stomach nor that it is released in amounts below 10%. This amendment with respect to the original teaching regarding the release substantially in the stomach thus involves a clear change in the technical content.

The feature that the 5-azacytidine is released in the stomach as defined in claim 1 of auxiliary requests 17, 20 and 23 may therefore not be directly and unambiguously derived from the original disclosure.

2.5.3 The patent proprietor argued with reference to the example of the expression "a tray plate with a substantially circular circumference" which according to the Guidelines for Examination in the EPO, F-IV 4.7, is to be interpreted as relating to the same technical feature as "a tray plate with a circular circumference" that the omission of the term "substantially" in claim 1 of auxiliary requests 17, 20 and 23 does not imply any change in technical teaching.

The Board observes, however, that the Guidelines explicitly refer to the cited example in the context of

the situation in which terms such as "substantially" or "approximately" are to be understood as qualifying a structural technical feature as being produced within the technical tolerance of the method used to manufacture it, unless the application suggests otherwise. As explained in section 2.5.2 above, in the present case the feature "substantially in the stomach" relates to a functional feature of the defined pharmaceutical composition for which the application as originally filed provides alternative specific meanings. The patent proprietor's argument is therefore not persuasive.

2.5.4 The Board therefore concludes that auxiliary requests 17, 20 and 23 do not comply with Articles 76(1) and 123(2) EPC.

2.6 Auxiliary requests 24-47

2.6.1 Auxiliary requests 24-47 were filed with the statement of grounds of appeal as a response to the finding in the decision under appeal that the feature "once per day" does not require administration on more than one day and is therefore anticipated by the administration of a single dose as described in document D9.

2.6.2 In its communication pursuant to Article 15(1) RPBA the Board expressed the preliminary opinion that auxiliary requests 24-47 were not to be admitted into the appeal proceedings under Articles 12(4) and 12(6) RPBA. The Board pointed out that the opposition division had already indicated in its preliminary assessment under Rule 116(1) EPC that the administration of a single dose described in document D9 involved the administration "once per day during one day" and therefore anticipated the feature of once per day

administration. Moreover, auxiliary requests 24-47 incorporated features only disclosed in the description of the application as filed, which raised additional and complex issues to be dealt with for the first time during the appeal proceedings.

2.6.3 No substantive arguments were submitted by the patent proprietor in response to the preliminary opinion regarding the admittance of auxiliary requests 24-47 expressed by the Board in its communication.

The Board has therefore not admitted auxiliary requests 24-47 into the appeal proceedings under Articles 12(4) and 12(6) RPBA for the reasons presented in section 2.6.2 above.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated