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Datasheet for the decision of 27 November 2023

Case Number: T 1221/21 - 3.3.07

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Title of invention:
THERAPEUTIC BENEFIT OF SUBOPTIMALLY ADMINISTERED CHEMICAL COMPOUNDS

Applicant:
Brown, Dennis M.

Headword:
Therapeutic benefit of chemical compounds / BROWN D.

Relevant legal provisions:
EPC Art. 83, 84
RPBA 2020 Art. 13(1), 13(2)

Keyword:
Claims - clarity - main request (no)
Sufficiency of disclosure - main request and auxiliary requests 1 to 21 (no)
Admittance of late-filed request - auxiliary request 22 (no)

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T 0492/92

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Case Number: T 1221/21 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 27 November 2023

Appellant: (Applicant)	Brown, Dennis M. 3475 Edison Way, Suite R Menlo Park, CA 94025 (US)
Representative:	Körfer, Thomas Mitscherlich PartmbB Patent- und Rechtsanwälte Karlstraße 7 80333 München (DE)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 25 March 2021 refusing European patent application No. 14782363.7 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	L. Basterreix

Summary of Facts and Submissions

I. The appeal was filed by the applicant (appellant) against the decision of the examining division to refuse European patent application No. 14 782 363.7 (hereinafter "the application").

II. The decision posted on 25 March 2021 was based on a main request filed on 23 April 2019 and 21 auxiliary requests, wherein auxiliary requests 1 to 2 were filed on 23 April 2019, auxiliary requests 3 to 8 were filed on 2 December 2019 and auxiliary requests 9 to 21 were filed on 8 January 2021.

III. The examining division decided in particular as follows:

(a) Claim 1 of the main request did not fulfill the requirements of Articles 83 and 84 EPC. This objection applied *mutatis mutandis* to claims 1 of auxiliary requests 2, 3, 5, 6, 8, 9 to 13, 15, 18, 19 and 21. The same reasoning of lack of sufficiency of disclosure also applied to the method claims 1 of auxiliary requests 1, 4, 7, 14, 17 and 20.

(b) Claim 3 of the main request did not fulfill the requirements of Article 84 EPC due to the use of unclear terms such as "derivative", "analog" or "prodrug" as well as the use of the unclear functional definition "agent for enhancing the activity or efficacy of the therapeutic agent" and of the unclear definition in terms of a result to be achieved of the claimed composition as a "composition to improve the efficacy and/or reduce

the side effects of drug therapy". This objection applied mutatis mutandis to claims 2 of auxiliary requests 2, 3, 5, 6, 8, 9, 13, 15, 16, 18 and 19 and to claims 2 of auxiliary requests 4, 7, 14, 17 and 20.

IV. On 26 July 2021, with the statement setting out the grounds of appeal, the appellant defended its case based on the main request and auxiliary requests 1 to 21 forming the basis of the impugned decision.

V. Oral proceedings were held *per* video conference on 27 November 2023. During the oral proceedings, the appellant submitted a further auxiliary request 22.

VI. The content of the claims upon which the present decision is based can be illustrated as follows:

Independent claims 1 and 3 of the **main request** read as follows:

"1. A method for preparation of a medicament comprising an alkylating agent selected from the group consisting of uracil mustard, 6-methyluracil mustard, 6-ethyluracil mustard, 6-propyluracil mustard, 4-chlorouracil mustard, 4-cyanouracil mustard,and 4-nitrouracil mustard, the medicament for drug therapy of a malignancy selected from the group consisting of chronic lymphocytic leukemia, follicular lymphoma, lymphocytic lymphoma, chronic myelogenous leukemia, polycythemia vera, ovarian carcinoma, and carcinoma of the lung, the method comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the drug therapy; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the drug therapy by production of the medicament, wherein the factor or parameter is selected from the group consisting of:

(i) dose modification;
(ii) route of administration;
(iii) schedule of administration;
(iv) selection of disease stage;
(v) patient selection;
(vi) patient/disease phenotype;
(vii) patient/disease genotype;
(viii) pre/post-treatment preparation;
(ix) toxicity management;
(x) drug combinations;
(xi) chemosensitization;
(xii) chemopotentiation;
(xiii) post-treatment patient management;
(xiv) drug delivery systems;
(xv) drug conjugate forms;
(xvi) prodrugs;
(xvii) multiple drug systems;
(xviii) biotherapeutic enhancement;
(xix) biotherapeutic resistance modulation;
(xx) radiation therapy enhancement;
(xxi) selective target cell population therapeutics; and
(xxii) use with an agent enhancing its activity."

"3. A composition to improve the efficacy and/or reduce the side effects of drug therapy comprising an alternative selected from the group consisting of:

(a) a therapeutically effective quantity of a prodrug of a therapeutic agent, wherein the prodrug of the

therapeutic agent possesses increased therapeutic efficacy or reduced side effects;

(b) a composition comprising:
(i) a therapeutically effective quantity of a therapeutic agent or a prodrug of a therapeutic agent; and
(ii) at least one additional therapeutic agent, therapeutic agent subject to chemosensitization, therapeutic agent subject to chemopotentiation, drug delivery system, or agent for enhancing the activity or efficacyof the therapeutic agent or the prodrug of a therapeutic agent of (a), wherein the composition possesses increased therapeutic efficacy or reduced side effects

(c) a therapeutically effective quantity of a therapeutic agent or a derivative, analog, or prodrug of a therapeutic agent that is incorporated into a dosage form, wherein the therapeutic agent or the derivative, analog, or prodrug of a therapeutic agent incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects; and

(d) a therapeutically effective quantity of a therapeutic agent or a prodrug of a therapeutic agent or that is subjected to a bulk drug product improvement, wherein the therapeutic agent or the derivative, analog, or prodrug of a therapeutic agent subject to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects;

wherein the therapeutic agent is an alkylating agent selected from the group consisting of uracil mustard, 6-methyluracil mustard, 6-ethyluracil mustard, 6-

propyluracil mustard, 4-chlorouracil mustard, 4-cyanouracil mustard, and 4-nitrouracil mustard; and

wherein the composition possesses increased therapeutic efficacy or reduced side effects for drug therapy of a malignancy selected from the group consisting of chronic lymphocytic leukemia, follicular lymphoma, lymphocytic lymphoma, chronic myelogenous leukemia, polycythemia vera, ovarian carcinoma, and carcinoma of the lung."

Independent claims 1 of **auxiliary requests 2, 3, 5, 6, 8 to 13, 15, 16, 18, 19 and 21** defined, as claim 1 of the main request, a method for the preparation of a medicament comprising an alkylating agent selected from the group consisting of uracil mustard and its specific derivatives listed in claim 1 of the main request, the medicament being for drug therapy of a malignancy, the method comprising the steps of (a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the drug therapy and (b) modifying said factor or parameter to improve the efficacy and/or reduce the side effects of the drug therapy wherein the factor is selected from the group including *inter alia*:

- patient selection (auxiliary requests 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 18, 19, 21),
- patient/disease genotype (auxiliary requests 2, 3, 5, 6, 8, 9, 10, 11, 12, 13, 15, 16, 18, 19, 21),
- chemosensitization (auxiliary requests 2, 3, 5, 6, 8, 9, 10, 11, 12),
- biotherapeutic enhancement (auxiliary requests 2, 3, 5, 6, 8, 9, 10, 11, 13, 15, 16, 18, 19, 21),

- biotherapeutic resistance modulation (auxiliary requests 2, 3, 5, 6, 8, 9, 10, 11, 13, 15, 16, 18, 19, 21), and/or
- use with an agent enhancing its activity (auxiliary requests 2, 3, 5, 6, 8, 9, 10, 11, 13, 15, 16, 18, 19, 21).

Independent claims 3 of **auxiliary requests 2, 3, 5, 6, 8, 9, 13, 15, 16, 18, 19 and 21** defined, as claim 3 of the main request, a composition to improve the efficacy and/or reduce the side effects of drug therapy comprising one of the alternatives of claim 3 of the main request, in particular:

- a therapeutically effective quantity of a prodrug of a therapeutic agent, which prodrug possess increased therapeutic efficacy or reduced side effects (auxiliary requests 2, 3, 5, 6, 8),
- a composition comprising an agent for enhancing the activity or efficacy of said therapeutic agent or its prodrug (auxiliary requests 2, 3, 5, 6, 8, 13, 15, 16, 18, 19, 21),
- a composition comprising a therapeutic agent subject to chemosensitization (auxiliary requests 2, 3, 5, 6, 8, 9), and/or
- a therapeutic agent or a prodrug thereof subjected to a bulk drug product improvement (auxiliary requests 2, 3, 5, 6, 8, 13, 15, 16, 18, 21).

Independent claims 1 and 2 of **auxiliary request 1** read as follows:

"1. A method to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy comprising the steps of:

(a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the drug therapy; and

(b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the drug therapy,

wherein the drug therapy comprises uracil mustard and

wherein the factor or parameter is selected from the group consisting of:

(i) dose modification;
(ii) route of administration;
(iii) schedule of administration;
(iv) selection of disease stage;
(v) patient selection;
(vi) patient/disease phenotype;
(vii) patient/disease genotype;
(viii) pre/post-treatment preparation;
(ix) toxicity management;
(x) drug combinations;
(xi) chemosensitization;
(xii) chemopotentiation;
(xiii) post-treatment patient management;
(xiv) drug delivery systems;
(xv) drug conjugate forms;
(xvi) prodrugs;
(xvii) multiple drug systems;
(xviii) biotherapeutic enhancement;
(xix) biotherapeutic resistance modulation;
(xx) radiation therapy enhancement;
(xxi) selective target cell population therapeutics; and
(xxii) use with an agent enhacing its activity; and

wherein the composition possesses increased therapeutic efficacy or reduced side effects for drug therapy of a malignancy selected from the group consisting of a leukemia other than chronic granulocytic leukemia, a lymphoma, polycythemia vera, and, a carcinoma."

"2. A composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy comprising an alternative selected from the group consisting of:

(a) a composition comprising:
(i) a therapeutically effective quantity of a therapeutic agent, wherein the therapeutic agent is uracil mustard; and
(ii) at least one therapeutic agent subject to chemosensitization, drug delivery system, or agent for enhancing the activity or efficacy of the therapeutic agent, wherein the composition possesses increased therapeutic efficacy or reduced side effects;

(b) a therapeutically effective quantity of uracil mustard that is incorporated into a dosage form, wherein the uracil mustard incorporated into the dosage form possesses increased therapeutic efficacy or reduced side effects as compared with an unmodified therapeutic agent; and

(c) a therapeutically effective quantity of uracil mustard or that is subjected to a bulk drug product improvement, wherein the uracil mustard subject to the bulk drug product improvement possesses increased therapeutic efficacy or reduced side effects."

Independent claim 1 of **auxiliary requests 4, 7, 14, 17, 20 and 22** defined, as claim 1 of auxiliary request 1, a method to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy, the method comprising the steps of (a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the drug therapy and (b) modifying said factor or parameter to improve the efficacy and/or reduce the side effects of the drug therapy wherein the drug therapy comprises uracil mustard and wherein the factor is selected from the group including *inter alia*:

- patient selection (auxiliary requests 4, 7, 14, 17, 20),
- patient/disease genotype (auxiliary requests 4, 7, 14, 17, 20, 22),
- chemosensitization (auxiliary requests 4, 7),
- biotherapeutic enhancement (auxiliary requests 4, 7, 14, 17, 20, 22),
- biotherapeutic resistance modulation (auxiliary requests 4, 7, 14, 17, 20, 22), and/or
- use with an agent enhancing its activity (auxiliary requests 4, 7, 14, 17, 20).

Independent claims 2 of **auxiliary requests 4, 7, 14, 17, 20 and 22** defined, as claim 2 of auxiliary request 1, a composition to improve the efficacy and/or reduce the side effects of suboptimally administered drug therapy comprising one of the alternatives of claim 2 of auxiliary request 1, in particular:

- a composition comprising an agent for enhancing the activity or efficacy of the therapeutic agent (auxiliary requests 4, 7, 17, 20), and/or
- a composition comprising uracil mustard subjected to bulk drug product improvement (auxiliary requests 4, 7, 14, 17, 20, 22).

VII. The appellant requested that the decision under appeal be set aside and that a patent be granted based on the main request filed on 23 April 2019 or that the patent be maintained on the basis of one of the auxiliary requests 1 to 22 filed respectively on 23 April 2019 (auxiliary requests 1 and 2), 2 December 2019 (auxiliary requests 3 to 8), 8 January 2021 (auxiliary requests 9 to 21) and 27 November 2023 (auxiliary request 22).

VIII. The arguments of the appellant, as far as relevant for the present decision, can be summarised as follows:

(a) The main request met the requirements of Articles 83 and 84 EPC.

The subject-matter of independent claims 1 and 3 was sufficiently disclosed.

The claimed alkylating agents and malignancies were known.

Furthermore, the factors listed in claim 1 were discussed in the description in paragraphs [0097] to [0464]. The skilled person would know from common general knowledge and information in the prior art how to test the influence of said factors on the claimed malignancies by routine measures. The method of claim 1 could thus be performed by the skilled person without undue burden.

Regarding the composition of claim 3, the skilled person would be able to prepare it and then determine whether it would be suitable to improve the efficacy and/or side effects of drug therapy

using well known criteria in the field of medicine and clinical trials. In particular a number of side effects in the treatment of cancers were well documented. The subject-matter of claim 3 could thus be performed by the skilled person without undue burden.

Moreover, the skilled person would be aware of possible prodrugs, derivatives and analogs of the claimed alkylating agents. The skilled person would furthermore have sufficient and well-known means at hand to determine wich agents could be used as agents "for enhancing the activity or efficacy of the therapeutic agent". The skilled person was also aware of "agents subjected to bulk drug improvement". These terms did therefore not introduce any lack of clarity or sufficiency of disclosure.

Additionally, for the requirement of sufficiency of disclosure to be met the mere plausibility that the claimed effect could be achieved was sufficient. This would be the case in the present application.

Finally, there was no evidence that any alternatives within the scope of the claims would be inoperable or would require undue experimentation for the skilled person to be carried out. The breadth of a claim alone was not a reason for its lack of sufficiency of disclosure.

(b) Auxiliary requests 1 to 21 fulfilled the requirements of the EPC for at least the same reasons as the main request. In particular some of the objected terms had been deleted in various auxiliary requests.

(c) Auxiliary request 22 was to be admitted into the appeal proceedings as an attempt to overcome the issues raised for the previous requests.

Reasons for the Decision

Main request

1. Article 83 EPC

1.1 Claim 1 of the main request relates to a method of preparation of a medicament for drug therapy of a malignancy selected from a specific list wherein:

- the medicament comprises an alkylating agent selected from a specific group, and
- the method comprises the steps of
  (a) identifying at least one factor or parameter associated with the efficacy and/or occurrence of side effects of the drug therapy, wherein the factor or parameter is selected from a list defined in claim 1, and
  (b) modifying the factor or parameter to improve the efficacy and/or reduce the side effects of the drug therapy.

Claim 1 is thus directed to a medical use of a medicament comprising a particular alkylating agent wherein particular effects are further claimed, namely improving the efficacy and/or reducing the side effects of the drug therapy.

1.2 Claim 3 of the main request is worded as a composition claim. Four alternative types of compositions (in terms of included components) are defined. The composition is

further defined in terms of an effect to be achieved, by the following two features:

- "composition to improve the efficacy and/or reduce the side effects of drug therapy" and
- "wherein the composition possesses increased therapeutic efficacy or reduced side effects for drug therapy of a malignancy".

It follows that also claim 3 encompasses the feature relating to the particular effects of improving the efficacy and/or reducing the side effects of the drug therapy.

1.3 As these effects are part of both independent claims, its achievement over the whole scope of the claims is to be assessed under Article 83 EPC for both claims 1 and 3.

1.4 The Board considers that the claims and the description do not provide sufficient guidance for the skilled person to carry out a method or prepare a composition which would fulfill the claimed effect for the reasons detailed in the following paragraphs (see 1.5 and 1.6).

1.5 Claim 1

1.5.1 Claim 1 defines a very broad list of factors to be modified in order to achieve the claimed effects. Furthermore these factors are only defined in general and to a large extent functional terms. Some more specific, but still very diverse, embodiments are provided in the description for each of these factors (see *e.g.* paragraphs [097] to [464]). However, these too general and diverse indications do not appear to enable the skilled person to determine which specific embodiment covered by the 22 factors defined in claim 1

should be modified, let alone in which manner, depending on the therapeutic agent used and the malignancy to be treated so as to successfully achieve any of the claimed effects.

1.5.2 Indeed the present application does not provide any practical example of a method according to claim 1 which would achieve the claimed effects nor any protocol and test to be followed to select and appropriately modify one of the claimed factors so as to achieve the claimed effects.

1.5.3 In this context the argument of the appellant, that the skilled person could find in the prior art for each factor methods allowing to measure the impact of said factor on the efficacy or side effects of a given therapy, is not convincing in the present case.

1.5.4 First of all, this argument has not been supported by any evidence, such as examples of prior art providing such methods.

1.5.5 Furthermore, while the Board does not deny that such methods may indeed be available in the prior art, their successful application in the present case requires far more than standard routine experimentation. The issue is indeed not for the skilled person to be able to measure the impact of some of the claimed factors on the claimed treatments but to determine how to achieve the claimed effects. The argument of the appellant relies on a try and see approach based on non defined methods allegedly available in the prior art. The very large number of possible factors (*i.e.* not merely the 22 generally and/or functionally defined factors of claim 1 but the actual specific physical parameters encompassed by these factors) combined with the variety

of active agents and malignancies to be tested, not to forget the various specific effects to be obtained (efficacy but also specific side effects, which are not defined in claim 1), actually render the amount of experimentation to be carried out undefinite.

1.5.6 As an illustration, when choosing chemosensitization as factor in claim 1, the description provides in paragraph [0124] a list of therapeutics to be used together with one of the 7 claimed alkylating agents as chemosensitizers. This list contains around 20 functionally defined agents which thus cover an undefinite number of structurally defined compounds. The application does not provide any further indication regarding how to select the combination of alkylating agent and further therapeutic agent for a given malignancy and a given effect to be achieved (improved efficacy or reduction of a still to be defined side effect). Thus the skilled person would be left to set up an assay based on some non-defined prior art disclosure to evaluate the potential effect of each and every combination of these undefinite agents with one of the claimed alkylating agent in achieving one of the claimed effects when used in the treatment of one of the 10 claimed malignancies. This implies over 1000 possible different tests to be carried out without any guidance as to how to put them into practice.

Similar examples can be made with each and every one of the 22 factors listed in claim 1, including *inter alia* patient selection (over 20 different types of examples of patient groups being generally defined in paragraph [110]), patient/disease genotype (no mention of specific genotypes but merely a list of around 10 general methods to determine a patient's genotype provided in paragraph [0114]), biotherapeutic

enhancement (list of 8 exclusively functionally defined therapeutics to be used together with one of the 7 claimed alkylating agents provided in paragraph [0154]) and biotherapeutic resistance modulation (list of 8 exclusively functionally defined types of resistance in tumors provided in paragraph [0156] for which the 7 claimed alkylating agents may be used).

1.5.7 Moreover for several of the claimed factors (*e.g.* "selection of disease stage", "patient/disease genotype", "post-treatment patient management", "radiation therapy enhancement") and/or when aiming at reducing side effects, extensive clinical trials may be required. Whether or not some examples of clinical trials may be accessible to the skilled person from databases, carrying out such experimentation without any further guidance in the context of the present specific case cannot be considered as mere routine work.

1.5.8 In the absence of any guidance regarding how to modify each and every claimed factor to successfully achieve the claimed effects, the skilled person willing to carry out the method of present claim 1 is ultimately faced with the undue burden of performing a research program.

1.5.9 The appellant argued that the fact that by modifying the claimed factors (such as dose administration or administration route), an effect on tumor growth (*i.e.* efficacy) or on side effects was plausible, was enough for the requirement of sufficiency of disclosure to be achieved. This argument is however not convincing in the present case.

The present application does not provide any kind of evidence, be it in the form of experimental data or mechanistic explanation, that any one of the claimed effects can be successfully achieved by the claimed method without undue burden.

While the requirements of Article 83 EPC may be fulfilled when the actual achievement of a claimed effect has been rendered plausible by experimental data or a technical concept disclosed in the application, it remains that the claimed invention must be sufficiently disclosed for the skilled person to put it into practice. In the present case, for the reasons detailed above (see 1.5.4 to 1.5.8), the present application fails to provide sufficient indication to the skilled person regarding how to carry out the claimed method so as to achieve the claimed effects. Even if it might have been plausible that out of all the conceivable combinations of parameters, therapeutic agents, malignancies and particular effects covered by the claims, some will be successful, this is not sufficient in the present case since as detailed above the guidance towards the appropriate method is missing.

1.6 Claim 3

1.6.1 Claim 3 defines a composition comprising:

- either an alkylating therapeutic agent (or a prodrug, analog, derivative thereof or that is subject to a bulk drug product improvement) selected from a list and which possesses increased therapeutic efficacy or reduced side effects *per se*,
- or a composition of an alkylating therapeutic agent selected from a list together with at least one additional therapeutic agent, wherein the

composition possesses increased therapeutic efficacy or reduced side effects.

1.6.2 There does not appear to be any evidence in the application (neither in the claims nor in the description) substantiating that any claimed alkylating agents *per se* would indeed possess the claimed effects.

According to the appellant, paragraph [2] as well as paragraphs [6] to [9] would indicate that uracil mustard and the claimed relating alkylating agents have an anti-cancer activity but may induce side-effects. The application would propose to identify and modify such factors that lead to the side effects. The application would thus provide a clear guidance to determine which alkylating agent possess the claimed effect.

The Board cannot however find in the cited paragraphs a teaching of which agent would indeed possess the claimed effects. Indeed, paragraph [2] merely defines the general field of the invention and paragraphs [6] to [9] relate to prior art disclosures in particular unsatisfactory clinical trials.

1.6.3 Furthermore there is no detailed information regarding how to select
(i) an appropriate prodrug, analog, derivative thereof or agent subject to bulk drug product improvement that would possess said effects, or
(ii) the at least one additional therapeutic agent, in particular the "agent for enhancing the activity or efficacy of the therapeutic agent or the prodrug of the therapeutic agent", that would result in a composition that would possess said effects.

While prodrugs, analogs or derivatives of the claimed alkylating agents as well as additional therapeutic agents in the field of malignancies treatment may be generally known to the skilled person, the skilled person would still not be in a position to determine which one may possess or lead to the claimed effects. The application lacks any guidance or specific test to this end.

1.6.4 Moreover the composition of claim 3 *per se* is defined as possessing increased therapeutic efficacy or reduced side effects. Apart from the features discussed above (see 1.6.2 and 1.6.3), the application does not teach any other features which would provide the claimed effects. Moreover, the present application does not provide any practical example of a composition according to claim 3 which would achieve the claimed effects.

1.6.5 Hence, the patent application does not enable the skilled person to prepare a composition according to claim 3 achieving the claimed effects without undue burden.

1.6.6 In this context, the appellant mentioned in the written proceedings that the expression "composition to improve the efficacy and/or reduce the side effects of drug therapy" in claim 3 should be read as a composition "suitable for" said technical effects (*i.e.* improvement of efficacy and/or reduction of side effects) and that such effects could be established following well-known criteria in the field of medicine and clinical trials. Furthermore a number of acceptable and non-acceptable side effects for the claimed therapy were well documented in the art.

This argument is not convincing. As already detailed above, no particular methods or protocols to assess the claimed effects are described in the application. Moreover in view of the variety of malignancies mentioned in the claims, it is to be expected that a variety of tests would be required as well, even more so if the assessed effect relates to the reduction of side effects which may be numerous and are also not defined in the claims. It follows that the try and see situation suggested by the appellant imposes an undue burden on the skilled person willing to carry out the invention.

In this context, during the written proceedings, the appellant further referred to T492/92 in which it was considered not needed to specify one of several known analytical methods. The Board however notes that the methods presently referred to are not mere common analytical methods but require *in vivo* testing and clinical trials. The conclusion drawn for analytical methods cannot therefore apply in the present case. In particular, contrary to the opinion of the appellant, the Board reiterates that such methods cannot be considered as routine testing.

1.7 The appellant also generally argued that there would be no evidence that alternatives within the scope of the claims would be inoperable or would require undue experimentation. The breadth of the claims alone would not constitute a lack of support or enablement.

While the Board agrees that the breadth of the claims *per se* might not result in a lack of support or of sufficient disclosure, the Board observes that neither the claims nor the description provide enough guidance for the skilled person to carry out the claimed

subject-matter. The guidance which the skilled person may find in the prior art in the form of *e.g.* clinical trials is broad and does not amount to routine testing. Since the subject-matter defined in the claims with respect to the factor to be modified (claim 1) or the agents to be used (claim 3) is very general and unspecific, the skilled person would not know how to select and apply any such potential guidance from the prior art. Finally it remains that when a therapeutic effect is claimed, the applicant bears the burden of proof regarding its achievement unless this is already known in the art. The present application does not provide any evidence of the achievement of the claimed effects with the claimed method and composition.

1.8 Accordingly, the main request does not comply with the requirements of Article 83 EPC.

2. Article 84 EPC

2.1 The terms "derivative", "analog" and the functional definition "agent enhancing the activity or efficacy of the therapeutic agent" and "agent subject to a bulk drug product improvement" used in the present claims (see independent claims 1 and 3) are not clear.

2.2 It is indeed not known to the skilled reader which structures are intended to be encompassed by the terms "derivatives", "analogs" and "agent subject to a bulk drug product improvement". The person skilled in the art cannot thus decide clearly which compounds are to be covered by the claims and which are not.

2.3 Furthermore the functional definitions "agent enhancing the activity or efficacy of the therapeutic agent" encompasses an undetermined number of compounds which

are defined only by reference to a desired functional activity. This functional definition does not give a specific technical guidance for ascertaining the scope of the claim as to which agents have the desired function, without imposing an unreasonable burden in contravention of Article 84 EPC.

2.4 The fact that, as brought forward by the appellant during oral proceedings, the skilled person may theoretically conceive some of such compounds is not sufficient for said claims to fulfill the requirements of Article 84 EPC as the claims have to be clear in themselves.

2.5 Accordingly, the main request does not meet the requirements of Article 84 EPC.

Auxiliary requests 1 to 21

3. The first independent claims of auxiliary requests 1 to 9 and 13 to 21 and the sole independent claims of auxiliary requests 10 to 12 share at least the following features with claim 1 of the main request:

> A method encompassing the steps (a) and (b) of claim 1 of the main request, *i.e.* identification and modification of a factor or parameter, wherein said factor or parameter is selected from *inter alia*:
> - patient selection (auxiliary requests 1 to 21),
> - patient/disease genotype (auxiliary requests 1 to 21),
> - chemosensitization (auxiliary requests 1 to 12),
> - biotherapeutic enhancement (auxiliary requests 1 to 11 and 13 to 21),

- biotherapeutic resistance modulation (auxiliary requests 1 to 11 and 13 to 21), and/or
- use with an agent enhancing its activity (auxiliary requests 1 to 11 and 13 to 21).

4. The second independent claims of auxiliary requests 1 to 9 and 13 to 21 share at least the following features with claim 3 of the main request:

A composition to improve the efficacy and/or reduce the side effects of drug therapy comprising one of the following alternatives:
- a therapeutically effective quantity of a prodrug of a therapeutic agent, which prodrug possesses increased therapeutic efficacy or reduced side effects (auxiliary requests 2, 3, 5, 6, 8),
- a composition comprising an agent for enhancing the activity or efficacy of said therapeutic agent or its prodrug (auxiliary requests 1 to 8, 13 and 15 to 21),
- a composition comprising a therapeutic agent subject to chemosensitization (auxiliary requests 2, 3, 5, 6, 8, 9), and/or
- a therapeutic agent or a prodrug thereof subjected to a bulk drug product improvement (auxiliary requests 1 to 8 and 13 to 21).

5. The appellant did not provide additional arguments specifically applying to the sufficiency of disclosure of these auxiliary requests. It follows that the reasoning developed for the main request concerning *inter alia* these features (see 1.1 to 1.7) apply *mutatis mutandis* to present auxiliary requests 1 to 21.

6. As a result, auxiliary requests 1 to 21 do not meet the requirements of Article 83 EPC.

Auxiliary request 22

7. Admittance

7.1 Auxiliary request 22 was filed during oral proceedings in the appeal proceedings. Its admittance into the appeal proceedings is to be decided on the basis of Articles 13(1) and 13(2) RPBA 2020.

7.2 Pursuant to Article 13(2) RPBA 2020, an amendment to the appellant's appeal case at this late stage of the proceedings shall not be admitted unless there are exceptional circumstances which have been justified with cogent reasons by the appellant.

In the present case, the appellant did not invoke any such exceptional circumstances. The Board observes in particular that all the issues discussed during oral proceedings had been raised in the impugned decision and in the two communications of the Board (pursuant to Article 100(2) EPC and Article 15(1) RPBA 2020) and no new issue was raised during the oral proceedings.

7.3 Furthermore pursuant to Article 13(1) RPBA 2020, in considering the admittance of an amendment to a patent application after the party has filed its grounds of appeal, the Board shall exercise its discretion in view of *inter alia* the suitability of the amendment to *prima facie* overcome the issues raised so far.

7.3.1 Independent claim 1 of auxiliary request 22 shares at least the following features with claim 1 of the main request:

A method encompassing the steps (a) and (b) of claim 1 of the main request, *i.e.* identification and modification of a factor or parameter, wherein said factor or parameter is selected from *inter alia*:
- patient/disease genotype,
- biotherapeutic enhancement, or
- biotherapeutic resistance modulation.

7.3.2 Independent claim 2 of auxiliary request 22 shares at least the following features with claim 3 of the main request:

A composition to improve the efficacy and/or reduce the side effects of drug therapy comprising a therapeutic agent (uracil mustard) subjected to a bulk drug product improvement.

7.3.3 It follows that this auxiliary request does not *prima facie* overcome the finding of lack of sufficiency of disclosure for the main request and auxiliary requests 1 to 21.

7.4 Hence, auxiliary request 22 is not admitted in the appeal proceedings (Articles 13(1) and 13(2) EPC).

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated