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Datasheet for the decision of 7 September 2021

Case Number:	T 0377/18 - 3.3.01
Application Number:	05792486.2
Publication Number:	1793824
IPC:	A61K31/44, A61K31/4415, A61K9/14, A61K9/16, A61K9/20, A61P35/00
Language of the proceedings:	EN

Title of invention:

NEW PHARMACEUTICAL COMPOSITIONS COMPRISING 4-(4-(3-(4-CHLORO-3-TRIFLUOROMETHYL-PHENYL)-UREIDO)-3-FLUORO-PHENOXY)-PYRIDINE-2-CARBOXYLIC ACID FOR THE TREATMENT OF HYPER-PROLIFERATIVE DISORDERS

Patent Proprietor:

Bayer HealthCare LLC

Opponent:

Ter Meer Steinmeister & Partner Patentanwälte mbB

Headword:

Regorafenib in solid dispersion/BAYER

Relevant legal provisions:

EPC Art. 56
RPBA 2020 Art. 13(2)

Keyword:

Inventive step - main request, auxiliary requests 1 to 5 (no)
Amendment after summons - taken into account - (no)
Admission of TIPA - (no)

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Case Number: T 0377/18 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 7 September 2021

Appellant: (Opponent)	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Strasse 4 80335 München (DE)
Representative:	Ter Meer Steinmeister & Partner Patentanwälte mbB Nymphenburger Straße 4 80335 München (DE)
Respondent: (Patent Proprietor)	Bayer HealthCare LLC 100 Bayer Boulevard Whippany, NJ 07981-0915 (US)
Representative:	Weickmann & Weickmann PartmbB Postfach 860 820 81635 München (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 28 November 2017 rejecting the opposition filed against European patent No. 1793824 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	M. Pregetter
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1793824 is based on European patent application No. 05792486.2, filed as an international application published as WO2006/026500.

The patent as granted contains several independent claims. Claim 1 as granted reads as follows:

"1. A composition comprising a solid dispersion comprising at least 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methyl amide in substantially amorphous form and a pharmaceutically acceptable matrix."

II. The following documents, cited during the opposition and appeal proceedings, are referred to below:

(2) WO2005/009961

(5) WO00/42012

(6) Leuner et al., Eur. J. Pharm. Biopharm., 2000, 50, 47-60

(14) "EMA approval on regorafenib for second-line treatment of adult patients with hepatocellular carcinoma (HCC), gastrointestinal stromal tumors (GIST) and colorectal cancer", submitted on 19 September 2017, 47 pages

(15) "Test Protocol", 6 September 2017, 10 pages

(18) Lowinger et al., Curr. Pharm. Des., 2002, 8, 2269-78

(19) EMA Assessment Report on Stivarga, 4 July 2017, 91 pages

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

In the course of the opposition proceedings, the patent proprietor requested that the opposition be rejected, and submitted auxiliary requests 1 to 4, all filed on 19 September 2017.

The opposition division rejected the opposition.

IV. The opponent (appellant) appealed against this decision.

V. With its reply to the statement setting out the grounds of appeal, dated 8 August 2018, the patent proprietor (respondent) resubmitted auxiliary requests 1 to 4 and submitted document (18).

Claim 1 of auxiliary request 1 differs from claim 1 as granted by the additional definition

"wherein the matrix comprises a pharmaceutically acceptable polymer, a sugar and/or sugar alcohol and/or cyclodextrin."

Claim 1 of auxiliary request 2 differs from claim 1 as granted by the definition that the matrix comprises a

"pharmaceutically acceptable polymer."

Claim 1 of auxiliary request 3 further limits this polymer to a polymer selected "from the group consisting of polyvinylpyrrolidone, vinylpyrrolidone/ vinylacetate copolymer, polyalkylene glycol, polyethylene glycol, hydroxyalkyl cellulose, hydroxypropyl cellulose, hydroxyalkyl methyl cellulose, hydroxypropyl methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, polymethacrylates, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol/vinyl acetate copolymer, polyglycolized glycerides, xanthan gum, carrageenan, chitosan, chitin, polydextrin, dextrin, starch and proteins."

Claim 1 of auxiliary request 4 provides a shorter list of polymers, the polymers being selected "from the group consisting of polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose and polyethylene glycole [sic]."

VI. On 7 February 2020 the board issued a summons to oral proceedings, followed on 7 April 2020 by a communication pursuant to Article 15(1) RPBA.

VII. On 24 June 2020 third-party observations including document (19) were submitted.

VIII. With a letter dated 16 July 2020, the respondent submitted auxiliary request 5.

Claim 1 of auxiliary request 5 is identical to claim 1 as granted.

IX. Oral proceedings before the board took place on 7 September 2021. During the oral proceedings, the respondent submitted auxiliary request 6.

Claim 1 of auxiliary request 6 differs from claim 1 as granted in that the matrix is restricted to polyvinylpyrrolidone.

X. The appellant's arguments, in so far as they are relevant to the present decision, may be summarised as follows:

Admission of third-party observations and document (19)

The third-party observations were to be admitted. According to established case law relevance was one of the criteria to consider. Furthermore, exceptional circumstances existed in view of the respondent's submission of document (18) and its claim of superiority of regorafenib over sorafenib in its submission of 8 August 2018. Document (19) was highly relevant, since it rebutted the respondent's arguments concerning superiority. As document (19) was published one year after the opposition had been filed, it could not have been submitted within the opposition period.

Inventive step

Document (5) represented the closest prior art. The general class of compounds of document (5), i.e. diaryl ureas, were known to be serine-threonine kinase inhibitors as well as tyrosine kinase inhibitors (paragraph [0002] of the patent in suit). Document (5) described its compounds as raf kinase inhibitors. The starting point for assessing inventive step was the compound disclosed as entry 49. It was supported by

case law that an embodiment could serve as a starting point. The difference between the subject-matter of claim 1 of the patent as granted and entry 49 was the fluorine substitution, instead of the chlorine substitution in the same position, and the formulation in amorphous form in a solid dispersion. Alternatively, the compound of entry 42 (sorafenib) could be seen as the starting point. The patent was silent on any effects linked to differences in structure. It merely referred to potential inhibitory actions of 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methyl amide (regorafenib), without providing any evidence thereof (paragraph [0004]). Such inhibitory action could thus not be acknowledged. Document (2), cited in paragraph [0004], was post-published and, moreover, not cited in the application as filed. As the patent was focused on compositions and not on the activity of an active compound, it contained no further relevant information. Document (14) was post-published and could not be taken into account in the absence of any initial plausibility. Even if it were taken into account, it could not show any superiority. The first partial problem was thus the provision of an alternative compound for the treatment of cancer. No effects had been shown over the closest prior art concerning the differences relating to the amorphous form and the solid dispersion. The presence or absence of certain molecular interactions that were possibly (not) present in the closest prior art could thus not be assessed. Moreover, the data in the patent in suit did not allow an effect to be established over the whole scope. The second partial problem was thus the provision of an alternative formulation. The solution to both partial problems was obvious. The structural aspects were obvious from document (5) itself, since it contained

"exemplified compounds" having either chlorine, methyl or hydrogen in the same position, thus pointing to substitutions in this position. As halogen substitutions were taught by document (5), the selection of a fluorine substitution in such a position was obvious. Concerning the formulation as a solid dispersion, this was obvious from document (6). Document (6) gave an overview of various compounds and thus showed the general applicability of solid dispersions to increase solubility and bioavailability of poorly soluble compounds. It also listed various carriers. The document provided motivation for the person skilled in the art to try solid dispersions for compounds such as regorafenib and sorafenib.

The carriers defined in the respective claims 1 of auxiliary requests 1 to 4 were taught by document (6).

Admission of auxiliary request 6

There were no exceptional circumstances justifying the admission of auxiliary request 6, which had been submitted at the latest possible stage.

XI. The respondent's arguments, in so far as they are relevant to the present decision, may be summarised as follows:

Admission of third-party observations and document (19)

The third-party observations should not be admitted. Article 115 EPC could not serve to extend a third party's rights beyond the rights of the parties to the proceedings. Document (19) was not only late-filed but furthermore post-published.

Inventive step

Document (5), which represented the closest prior art, disclosed a generic formula and 103 examples, none of which was highlighted, including sorafenib and its chlorine derivative. Various oral formulations of the compounds as such or their salts were suggested, including tablets, hard gelatin capsules, suspensions, oily suspensions and so on, without however mentioning solid dispersions. Document (2), cited in paragraph [0004] of the patent, showed that regorafenib inhibited the kinases mentioned in this paragraph. Document (2) was from the same applicant and had been published before the filing date of the patent. It thus proved that the patent proprietor had been in possession of the invention at the priority date. Document (14) disclosed that regorafenib was even effective in patients who showed insufficient response to the treatment with sorafenib, which is mentioned in document (5) as entry 42. It was thus clear that regorafenib had a different activity from sorafenib. With the reply to the statement setting out the grounds of appeal, evidence was provided that regorafenib showed an improved performance in inhibiting p38, mPDGFR and mVEGFR2, inhibiting and preventing the proliferation of MDA-MB231 cells, and was a more potent inhibitor in the PDGFR cellular assay than entry 49 of document (5) (Tables 1 and 2). The data in the patent in suit showed the improved solubility and bioavailability of regorafenib in solid dispersions (Examples 18 to 20, supplemented by the data in document (15)). The technical problem was thus the provision of (I) an oral formulation having improved solubility of (II) a carboxyaryl-substituted diphenyl urea with improved kinase inhibition activity. It was hindsight to arrive at regorafenib, after making

several selections for various substituents, when starting from document (5). There was no indication in document (5) that regorafenib would be well-suited for therapeutic use. Due to its fluorine substitution and the aromatic rings, regorafenib was very insoluble. Document (5) pointed to the use of salts, which is an option the person skilled in the art would try first, and disclosed galenic forms such as hard gelatin capsules. From the disclosure of document (5) regarding formulations, the person skilled in the art would not have envisaged the use of solid dispersions. Again, only hindsight would lead the person skilled in the art to consider solid dispersions, as no information could be found anywhere that regorafenib was a candidate for solid dispersions. As already stressed in the abstract of document (6), 40 years of research into solid dispersions had resulted in only a few marketed products, a trend that had not been broken even in 2021. Furthermore, document (6) did not disclose solid dispersions with active agents that were structurally or functionally related to regorafenib, and therefore provided no hint to the person skilled in the art. Moreover, document (6) raised certain concerns: it indicated that solid dispersions might not work, that formulations might be too large to be administered orally and that there were issues with predictability of results, in particular *in vivo* results (page 58, left-hand column). In sum, document (6) could not raise any expectation of success. Consequently, the person skilled in the art would not have arrived at regorafenib and would not have formulated it as a solid dispersion.

There were no additional arguments for auxiliary requests 1 to 5.

Admission of auxiliary request 6

Auxiliary request 6 was to be admitted. It corresponded to auxiliary request 4 limited to merely polyvinylpyrrolidone. The reason for its late submission was the surprising finding of the board concerning inventive step for the higher-ranking requests. This could not have been anticipated by the respondent in view of the rejection of the opposition by the opposition division and the lack of any indication of problems relating to patentability in the board's communication pursuant to Article 15(1) RPBA.

XII. The final requests of the parties were as follows:

The appellant requested that the decision under appeal be set aside and the patent be revoked. It also requested that the observations by a third party, including document (19), be admitted into the appeal proceedings, and that auxiliary request 6 not be admitted.

The respondent requested that the appeal be dismissed. Alternatively, it requested that the patent be maintained based on the claims of any of auxiliary requests 1 to 4 filed with the reply to the grounds of appeal, or of auxiliary request 5 filed by the letter dated 16 July 2020, or of auxiliary request 6 filed during the oral proceedings on 7 September 2021. The respondent further requested that the observations by a third party not be admitted into the appeal proceedings, and that auxiliary request 6 be admitted.

Reasons for the Decision

1. The appeal is admissible.

2. *Admission of the third-party observations and document (19)*

The third-party observations, including document (19), were submitted on 24 June 2020, more than 2 months after the board had issued a communication pursuant to Article 15(1) RPBA 2020 and more than 4 months after notification of the summons to oral proceedings, and thus at a very late stage.

According to Article 13(2) RPBA 2020, any amendment to a party's appeal case made after notification of a summons to oral proceedings shall, in principle, not be taken into account unless there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

The third party did not identify any exceptional circumstances. The appellant identified the respondent's line of argument in the reply to the statement setting out the grounds of appeal and the submission of document (18) as exceptional circumstances. The board cannot accept this argument. The third-party observations were submitted on 24 June 2020, almost two years after the reply to the grounds of appeal, which was submitted on 8 August 2018. Consequently, the submission of the third-party observations cannot be seen as a direct reaction to this reply. The (potential) relevance of

the third-party observations or of document (19) does not on its own constitute exceptional circumstances. In addition, a third party is not an actual party to the proceedings, and as such should not be accorded more favourable treatment than an actual party.

Consequently, the third-party observations submitted on 24 June 2020 were not admitted into the proceedings.

3. *Main request (patent as granted) - inventive step*

3.1 The patent in suit relates to pharmaceutical compositions and to their use for treating hyper-proliferative disorders, such as cancer, either as a sole agent or in combination with other therapies (paragraph [0001]). To this end, a composition comprising a solid dispersion comprising at least 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methyl amide (regorafenib) in substantially amorphous form and a pharmaceutically acceptable matrix is employed. The description states that diaryl ureas are a class of serine-threonine kinase inhibitors as well as tyrosine kinase inhibitors and are used as active ingredients in pharmaceutical compositions for the treatment of hyper-proliferative diseases, such as cancer. Regorafenib, in particular, has been discovered to be a potent inhibitor of raf, VEGFR-2, p38 and PDGFR kinases. These enzymes are said to be molecular targets of interest for the treatment of hyper-proliferative diseases, including cancer (paragraphs [0002] and [0004]). The oral route of drug administration is advantageous, and improved dissolution, superior absorption and increased bioavailability result from the invention (paragraphs [0005] to [0007]). Second-line treatments are not

mentioned.

3.2 It is common ground that document (5) represents the closest prior art.

Document (5), cited as background art in the application as filed on page 2, line 1, relates to the use of a group of diaryl ureas in the treatment of raf-mediated diseases (raf being a serine-threonine kinase), such as cancer, and to pharmaceutical compositions for use in such therapy. It was common ground that regorafenib came under Formula I of document (5). The compounds described under entries 42 and 49 differ from regorafenib only in a substitution on one of the aryl rings (being hydrogen or chlorine instead of fluorine). Information on the substitution by halogens, including fluorine, chlorine, bromine and iodine, can be found on page 4, lines 12 to 14 and page 6, lines 5 to 8. Concerning the formulation of these actives, some general information is given on page 10, line 10 to page 12, line 29. Solid dispersions are not mentioned.

Concerning the precise starting point in document (5), the following applies. The Markush formula denominated "Formula (I)" describes the broadest teaching of this document. Indications as to how the substituents may be selected can be found in the specific compounds described in the section "Synthesis of Exemplified Compounds" (starting on page 53) and in Tables 1 to 6. A total of 103 compounds are individualised. Their depiction in Tables 1 to 6 clearly shows which positions for substitution and which substituents are particularly envisaged in order to obtain compounds for the treatment of cancer. Consequently, either Formula (I) or any of the 103 compounds, in particular

the closely-related compounds of entries 42 and 49, can be taken as the starting point in the present case.

3.3 Starting from any point in document (5), the differences are the structure of the active agent and the formulation of the active agent in amorphous form as a solid dispersion.

3.3.1 Firstly, it will be discussed whether any surprising effect can be acknowledged to be linked to the difference in structure.

The application as filed does not explicitly identify any surprising effects linked to the structure of the active agent.

The respondent pointed to paragraph [0004] of the patent in suit, where four kinases, raf, VEGFR-2, p38 and PDGFR, are listed, and to the reference to document (2) in that paragraph. According to the respondent, the reference to document (2) showed that regorafenib did indeed inhibit the listed kinases and that this knowledge had been in the possession of the patent proprietor at the filing date of the patent application underlying the patent in suit. Furthermore, it pointed to the data in the reply to the grounds of appeal and to the disclosure of document (14). The four kinases of paragraph [0004] are described as being "molecular targets of interest for the treatment of hyper-proliferative diseases, including cancer". The first kinase listed, raf, is at the heart of the disclosure of the closest prior art. No information is provided as to whether regorafenib is capable of inhibiting raf or any of the other three kinases in a way different from the cited background art (including document (5)) and/or whether such inhibition would lead

to any improvement in the treatment. In fact, the application as filed contains no statement relating to and no data confirming the extent of the inhibition or indicating that this inhibition would lead to an improvement in the treatment of any hyper-proliferative disease. The appellant has furthermore pointed to the fact that there was no evidence that regorafenib inhibited these four kinases at all.

Document (2) was not cited or mentioned in any other way in the application as filed. Its contents, including the data presented, do not form part of the disclosure of the application as filed (or of the patent as granted). Consequently, document (2) is to be treated in the same way as any other post-published document. The fact that it has the same applicant as the patent in suit is irrelevant in the context of the present decision. When the disclosure of document (2) is disregarded, there is indeed no evidence in the application as filed that regorafenib inhibits raf, VEGFR-2, p38 and PDGFR. The application as filed, however, also includes a background section, in which various publications, including document (5), are discussed as disclosing diaryl ureas as serine-threonine kinase inhibitors as well as as tyrosine kinase inhibitors. Consequently, a person skilled in the art would have considered it plausible that a further diaryl urea, structurally closely resembling the compounds exemplified in document (5), might have similar activity. On the other hand, it cannot be derived from the application as filed that regorafenib had a pattern of inhibition different from these structurally closely-related compounds. Such a pattern of inhibition thus cannot represent a surprising technical effect.

Document (14) does not bear a publication date. It states on page 27 that the date of the first [marketing] authorisation of Stivarga (regorafenib) was 26 August 2013. The respondent, in its letter dated 19 September 2017, states that EMA approval was issued in August 2017. There is no information on file that would lead to the conclusion that document (14) was published before the effective date and none of the parties has argued in this direction. Document (14) is thus treated as a post-published document. According to the respondent, this document shows that "regorafenib was even effective in patients who showed insufficient response to the treatment with sorafenib" (entry 42 of document (5)). The appellant stated that document (14) did not show superiority of regorafenib over sorafenib. The board takes the statement made on page 2, point 4.1 of document (14), that one of the therapeutic indications was a monotherapy for the treatment of adult patients with "- hepatocellular carcinoma (HCC) who have been previously treated with sorafenib", to mean that regorafenib was indicated as a second-line treatment when treatment with sorafenib was no longer possible. However, in the absence of any indication in the application as filed that regorafenib could be used upon failure of treatment with other actives of the same chemical class, i.e. diaryl ureas discussed in the background section with reference to document (5), such post-published evidence cannot be taken into account for assessing inventive step.

In addition, in its reply to the grounds of appeal, the respondent presented data which according to it demonstrated the superiority in activity of regorafenib as compared with compound 49 (Tables 1 and 2). Having been submitted for the first time in the reply to the grounds of appeal, the data are clearly post-published.

As they present data on an effect that cannot be derived from the application as filed, despite document (5) being discussed in the background section, the data are to be disregarded.

Neither the information of documents (2) and (14), nor the data contained in the reply to the grounds of appeal, nor a statement summarising the results of these sources of information and indicating their relevance, was available before the effective date. Furthermore, although document (5) is disclosed in the description as background art, no advantageous effects of the invention are discussed with regard to document (5) and its raf kinase inhibitors (or in view of any other document mentioned in the background section).

The board thus comes to the conclusion that an improvement over the compounds of document (5) was neither foreshadowed, nor alleged, nor shown in the application as filed. Document (5) is not merely a document that could have been considered by the patent proprietor (or the then applicant) when drafting the application, but a document that actually was considered as can be seen by its being cited in the background section. Since, as a consequence, post-published evidence cannot be taken into account, none of the effects related to improved treatment (different pattern of inhibition, second-line treatment, higher levels of inhibition) can be considered when applying the problem-solution approach.

3.3.2 Secondly, attention is paid to the effects linked to the formulation of the amorphous active agent as a solid dispersion.

The patent in suit provides data in example 18 showing that solid dispersions of regorafenib in polyvinylpyrrolidone (PVP) lead to better drug dissolution in a particular aqueous medium than a physical mixture of the two components. Similar data for other excipients can be found in document (15). Examples 19 and 20 show the corresponding improved bioavailability for the drug from solid dispersions. The data thus prove that solid dispersions comprising regorafenib are suitable galenic forms capable of delivering regorafenib to a patient.

The parties disagreed as to whether these data showed an improved effect over the closest prior art.

In the situation at hand, it is as a matter of principle not possible to provide a valid comparison for the galenic component of the pharmaceutical composition with the closest prior art. The reason for this is that the compound under consideration has not been individualised in the closest prior art and galenic issues relate primarily to the compound and its interaction (due to its physicochemical properties which are determined by its molecular structure) with its environment, be it with the excipients in the pharmaceutical formulation or with the parts of the patient's body during the absorption process. The data of the patent and of document (15) show, however, that not all galenic forms lead to the same solubility and the same bioavailability and thus are not equally suitable.

3.4 It follows that the technical problem is the provision of a further active agent for use in the treatment of hyper-proliferative diseases which is formulated in a form which allows sufficient bioavailability.

The problem has been solved: this has not been contested.

3.5 It remains to determine whether the solution is obvious.

3.5.1 A galenic form can only be provided and tested for its suitability once an active agent has been chosen. Therefore the examination of obviousness will first focus on the active agent.

It has been determined under point 3.3.1 above that no surprising effect has been linked to the fluorine substitution that distinguishes regorafenib from some of the compounds exemplified in the closest prior art document (5). It is furthermore common ground that regorafenib comes under the Markush formula defined in document (5). The person skilled in the art, starting from document (5) and aiming at providing a further active agent for the treatment of hyper-proliferative diseases, would have considered any of the compounds, and in particular compounds that are structurally closely related to compounds exemplified in this document. Consequently, the person skilled in the art would have arrived at the claimed compound.

3.5.2 Having settled on one of the compounds which come under the teaching of the closest prior art, the person skilled in the art would have been faced with the need to select a suitable galenic form.

Various galenic forms are known in the art: a person skilled in the art would have chosen a particular one based on their knowledge of the physicochemical properties of the compound to be formulated and on the

desired route of administration. Further issues might be a particular pattern of release (e.g. delayed or sustained release). One of the crucial physicochemical properties of a novel drug substance is its solubility. Solubility is thus the property of a novel active agent to which a person skilled in the art would have paid particular attention and that would have been foremost in their consideration for selecting an appropriate galenic form.

It was common ground that a person skilled in the art would have been aware that, due to their chemical structure, which includes aromatic rings and halogen substitution, the compounds of document (5) are poorly soluble under physiological conditions. A person skilled in the art would thus have started their routine tests with galenic forms known to be particularly suitable for poorly water-soluble active agents.

A document dealing with the formulation of such poorly water-soluble active agents is on file as document (6). Document (6) is a review article, and thus an article summarising the state of the art in relation to its topic. It is entitled "Improving drug solubility for oral delivery using solid dispersions". In its abstract it stresses the challenging aspects in formulation development caused by the solubility behaviour of drugs. It goes on to state that the number of poorly water-soluble compounds in this field has increased. The purpose of the article is identified as giving an overview of the historical background of various systems and especially as providing information on various aspects of solid dispersions. On page 47, it identifies physical properties of the solid drug itself (e.g. increase in available surface area, see Table 1)

but goes on to propagate that formulation approaches are "the most attractive option for increasing the release rate" (page 47, right-hand column, last sentence of the full paragraph). In section 3.2 carriers for providing the matrix of the solid dispersion of the drug are described. Various aspects are discussed, such as molecular weight and solubility in water and organic solvents. The link between release rate from the solid dispersion and bioavailability is addressed (e.g. page 53, left-hand column, first full paragraph). Polyethylene glycol, polyvinylpyrrolidone, cellulose derivatives such as hydroxypropyl methyl cellulose and hydroxypropyl cellulose, and sugars, polyols and their polymers (sections 3.2.1 to 3.2.7) are discussed as possible carriers. The review article ends with a summary, in which some concerns related to solid dispersions are enumerated. Among these concerns is the possibility that the amount of dispersion required to administer the usual dose of the drug may be too high to produce a tablet or a capsule that can be easily swallowed, or that the correlation between *in vitro* and *in vivo* release from the solid dispersion might not be sufficient to lead to adequate bioavailability (page 58, left-hand column, first paragraph).

Document (6) thus clearly teaches that solid dispersions are a galenic form worth exploring when trying to provide a formulation of a poorly soluble drug. It encompasses several concrete proposals for carriers. The person skilled in the art would have interpreted the concerns addressed in the final parts of document (6) as meaning that there was no certainty of success. However, these concerns would not have deterred the person skilled in the art from seriously considering a galenic form that has been described as

advantageous for precisely such poorly soluble drugs as regorafenib. Consequently, the person skilled in the art would have seriously contemplated solid dispersions in their routine tests to find a formulation for regorafenib.

Furthermore, document (6) suggests trying to modify the crystal habit of the active compound (Table 1). A person skilled in the art would thus include variations of the crystal habit, including the amorphous form, in their routine tests without exercising inventive skill.

Finally, it must be stressed that in the case at hand the issue to be decided on is merely which galenic forms a person skilled in the art would have taken into consideration when setting up their routine tests for determining an appropriate galenic form. As no galenic formulation for regorafenib had existed at the effective date, the problem, as a matter of principle, cannot be seen as providing an improved galenic formulation.

The subject-matter of claim 1 of the main request (patent as granted) does not involve an inventive step (Article 56 EPC).

3.5.3 *Further arguments*

(a) The respondent argued that document (5) points to salts, implying that solubility problems would mainly be dealt with by providing more-soluble forms of the active agents.

Salts are clearly one of the options a person skilled in the art would consider, see Table 1 of document (6). However, as can be seen from the

patent in suit, see for example paragraphs [0010] and [0011] and claims 7 and 8, active agents in the form of salts and solid dispersions are not mutually exclusive. The mere fact that several options were at their disposal does not mean that the skilled person would have restricted their routine tests to one particular option and disregarded other options.

(b) The respondent argued that in 2021 there were still hardly any drugs marketed as solid dispersions. Solid dispersions were complex to handle ("aufwändig") and a person skilled in the art would only have considered using them in exceptional circumstances ("Notfall").

The board follows the teaching of document (6) that explicitly aims at providing formulations for poorly water-soluble compounds and clearly refers in its abstract to the "challenging" aspects of solubility behaviour of drugs in formulation development. The wording used in this abstract clearly establishes that poorly water-soluble compounds may need exceptional solutions with regard to their formulation. Furthermore, considerations extending up to 2021 cannot be taken into account when assessing inventive step of a patent with an effective date 15 years earlier.

(c) In addition, the respondent argued that document (6) did not disclose solid dispersions with active agents that were structurally or functionally related to regorafenib.

The board draws attention to the abstract of document (6), which identifies the solubility

behaviour as the determining factor. There is no structural or functional discussion of the compounds disclosed in document (6) in connection with their suitability for being formulated in solid dispersions. The exemplified drugs are varied in structure and functionality (see statement setting out the grounds of appeal, point 2.5).

4. *Auxiliary requests 1 to 5 - inventive step*

The subject-matter of claim 1 of auxiliary requests 1 to 4 differs from the subject-matter of claim 1 of the patent as granted in the definition of the matrix. The carriers forming the matrix and representing the limitations applied in these claims are discussed in detail in document (6) (see point 3.5.2 above). Consequently, the line of reasoning given for claim 1 of the patent as granted applies *mutatis mutandis* to the subject-matter of these claims.

The subject-matter of claim 1 of auxiliary request 5 is the same as the subject-matter of claim 1 as granted. The reasoning of point 3. applies.

The subject-matter of claim 1 of auxiliary requests 1 to 5 does not involve an inventive step (Article 56 EPC).

5. *Auxiliary request 6 - admission*

Auxiliary request 6 was submitted at a very advanced stage of the appeal proceedings, namely at the oral proceedings before the board and after the discussion of inventive step for the main request and for auxiliary requests 1 to 5. The board does not consider that a new situation had arisen during the oral

proceedings which might be considered as exceptional circumstances justifying the filing of this request. The fact that a board, on the basis of arguments presented by a party, might take a different view from the department whose decision is appealed cannot be considered a surprising event as it is one of the two possibilities. As the patent proprietor is the party that is solely responsible for determining the text of the patent (see Article 113(2) EPC), it is however obliged to submit amendments or possible fall-back positions. For reasons of procedural economy and fairness to the other party this must be done at the earliest possible opportunity, as reflected in the RPBA.

As the appellant had failed to present exceptional circumstances which justified the filing of amendments during the oral proceedings and after the discussion of inventive step, the board decided not to admit auxiliary request 6 into the appeal proceedings (Article 13(2) RPBA).

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

M. Schalow T. Sommerfeld

Decision electronically authenticated