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Application No. / Patent No. 12 888 899.7 - 1109 / 2 922 818 /	Ref. P126185EPPC/DLB	Date 01.03.2022
Proprietor Hangzhou Dac Biotech Co., Ltd		

Decision revoking the European Patent (Art. 101(3)(b) EPC)

The Opposition Division - at the oral proceedings dated 27.09.2021 - has decided:

European Patent No. EP-B- 2 922 818 is revoked.

The reasons for the decision are enclosed.

Possibility of appeal

This decision is open to appeal. Attention is drawn to the attached text of Articles 106 to 108 and Rules 97 to 98 EPC.

Opposition Division:

**EX1079
SYNAFFIX B.V.
IPR2022-01531**

Chairman: Kardinal, Siegmар
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Enclosure(s): 21 page(s) reasons for the decision (Form 2916)
Wording of Articles 106 - 108 and Rules 97-98 EPC (Form 2019)
Minutes of oral proceedings
Main Request; Auxiliary Requests 0A-0C, 1, 1A-1C, 2, 2A-2C, 3, 3A-3C, 4, 4A-4C, 5, 5A-5C, 6, 6A-6C, 7, 7A-7C, 8, 8A-8F, 9, 9A-9C, 10, 10A-10C, 11, 11A-11C, 12, 12A-12C
to EPO postal service: 24.02.22

I. Summary of Facts and Submissions

1. European patent 2 922 818 having the title "HYDROPHILIC LINKERS AND THEIR USES FOR CONJUGATION OF DRUGS TO CELL BINDING MOLECULES" is based upon European patent application No. 12 888 899.7 which was filed on 24 November 2012 as international application No. PCT/IB2012/056700 and published as WO 2014/080251. The mention of the grant of the patent has been published in the European Patent Bulletin of 5 September 2018. Proprietor of the patent is

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2. Notices of opposition have been filed by

Opponent 1:
Strawman Limited
Orchard Lea
Horns Lane
Combe, Witney
Oxfordshire OX29 8NH
GB

on 31 May 2019 and by

Opponent 2:
Maschio & Soames IP Limited
30 Carlton Crescent
Southampton SO15 2EW
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on 3 June 2019.

Both Opponents have requested the revocation of the patent in its entirety based on lack of novelty (Art. 100(a), 52(1) and 54 EPC), lack of inventive step (Art. 100(a), 52(1) and 56 EPC) and lack of sufficient disclosure (Art. 100(b) and 83 EPC). The ground of added subject-matter (Art. 100(c) and 123(2) EPC) was raised by Opponent 1; Opponent 2 has ticked the corresponding box in Form 2300E, but has not provided any arguments in this respect in the notice of opposition. Opponent 1 has filed documents

D1-D9 in support of the opposition, Opponent 2 documents D8 and D10-D17 (see section 19 below for a consolidated list of cited documents). Oral proceedings were requested auxiliarily by both Opponents.

3. In a letter received on 30 October 2019, the Proprietor has requested the maintenance of the patent on the basis of a new Main Request or one of Auxiliary Requests 1-6. Oral proceedings were requested auxiliarily.

4. On 2 March 2020, the Division issued summons to attend oral proceedings on 23 and 24 November 2020.

5. On 31 March 2020, Opponent 1 provided written submissions accompanied by documents D18-D25.

6. On 15 July 2020, Opponent 2 filed documents D26 and D27.

7. On 12 August 2020, Opponent 1 provided written submissions accompanied by document D28.

8. On 23 September 2020, Opponent 2 provided written submissions.

9. On 23 September 2020, the Proprietor provided written submissions and filed an amended Main Request and Auxiliary Requests 1-11. It was requested not to admit D26 and D28 into the procedure.

10. On 14 October 2020, the parties were notified by e-mail, after agreement had been obtained by e-mail, that the oral proceedings on 23 and 24 November 2020 would be held as a videoconference.

11. On 27 October 2020, the Proprietor withdrew the agreement to hold the oral proceedings by videoconference and requested rescheduling of the oral proceedings to a point of time not before the end of March 2021.

12. On 28 October 2020, Opponent 1 requested that the Proprietor's request not to hold the oral proceedings by videoconference on 23 and 24 November 2020 be refused. Opponent 2 filed a corresponding request on 5 November 2020.

13. On 6 November 2020, the Division informed the parties that the summons to attend oral proceedings on 23 and 24 November 2020 had been cancelled. On 12 January 2021, the Division issued new summons to attend oral proceedings by videoconference on 27 and 28 September 2021.

14. On 5 May 2021, Opponent 1 provided written submissions accompanied by document D29.

15. On 13 July 2021, Opponent 2 provided written submissions.

16. On 26 July 2021, the Proprietor provided written submissions accompanied by a new Main Request and Auxiliary Requests 0A-12C and document D30.

17. On 21 September 2021, Opponent 1 requested not to admit the requests submitted on 26 July 2021 into the procedure.

18. Oral proceedings were held on 27 September 2021. During the oral proceedings, the Proprietor filed Auxiliary Requests 8D-8F which the opponents requested not to admit. At the end of the oral proceedings, the Division's decision was announced to revoke the patent.

19. The following documents have been submitted.

D1	WO 2012/145112 A2
D2	US 4227918 A
D3	Brouwer et al., Bioorg. Med. Chem. (2007), 15(22), 6985-6993
D4	Block et al., Tetrahedron (2004), 60(35), 7525-7541
D5	WO 2008/015415 A2
D6	Morales-Sanfrutos et al., J. Org. Chem. (2010), 75(12), 4039-4047
D7	Morales-Sanfrutos et al., Org. Biomol. Chem. (2010), 8, 667-675
D8	WO 02/087497 A2
D9	Temming et al., Bioconjugate Chem. (2006), 17(6), 1385-1394
D10	WO97/41897
D11	US5094848
D12	WO2009/134976
D13	WO2009/134977
D14	EP1625857
D15	Robert Y. Zhao et al., Journal of Medicinal Chemistry (2011), vol. 54, 3606-3623
D16	US6214345
D17	Industrial Solvents Handbook, Marcel Dekker Inc. (2003), 92

D18	WO 2012/153193 A2
D19	Tsuchikama et al., Protein Cell (2018), 9(1), 33-46
D20	VanBrunt et al., Bioconjugate Chem. (2015), 26(11), 2249-2260
D21	Mamidyala et al., Chem. Soc. Rev. (2010), 39, 1252-1261
D22	Meldal et al., Chem. Rev. (2008), 108, 2952-3015
D23	Wang et al., J. Biochem. (1994), 115(5), 898-903
D24	Straus et al., Histochemistry (1986), 85(4), 277-285
D25	Straus et al., Histochemistry (1987), 86(5), 453-457
D26	Llewelyn et al., The Lancet (2002), 2, 156-162
D27	Ullmann's Encyclopedia of Chemistry (2002), 34, 711
D28	US 2004/0185053 A1
D29	Langford et al., Ann. Intern. Med. (1998), 129(1), 49-58
D30	Wikipedia entry "Mertansine"

II. Reasons for the Decision

1. Admissibility of the Oppositions

The oppositions meet all of the requirements of Art. 99(1) and 100 and R. 3(1) and 76(1) and (2) EPC and are thus admissible.

2. The Cancellation of the Oral Proceedings on 23 and 24 November 2020

Oral proceedings by videoconference had been scheduled for 23 and 24 November 2020 with the consent of all parties. On 27 October 2020, the Proprietor withdrew the agreement to hold the oral proceedings by videoconference and

requested rescheduling of the oral proceedings. On 28 October 2020, Opponent 1 requested that the Proprietor's request not to hold the oral proceedings by videoconference on 23 and 24 November 2020 be refused. Opponent 2 filed a corresponding request on 5 November 2020.

For the oral proceedings scheduled for 23 and 24 November 2020, the Decision of the President of the EPO dated 14 April 2020 concerning the pilot project for oral proceedings by videoconference before opposition divisions applied. According to Art. 2(1) of this decision, the agreement of all parties was necessary for a videoconference. The Division considered that, after the withdrawal of the Proprietor's consent, it was impossible to comply with this requirement while maintaining the oral proceedings by videoconference on the planned date. The oral proceedings thus had to be postponed irrespective of whether, as stated by Opponent 1, the Proprietor's representative should be able to join a videoconference even under the situation of the pandemic at the time and the withdrawal of consent occurred at a very late stage. The Division also does not agree with Opponent 2's conclusion that, due to the Proprietor's statement that it was not in principle opposed to oral proceedings by videoconference, there was actually an implicit consent and the Proprietor in effect had merely requested a change of date. The Proprietor's comments as to the possibility of a videoconference in general cannot be understood to override the explicit withdrawal of agreement to a videoconference on the specific date in question.

The Division thus considers that the oral proceedings had to be postponed.

3. Admissibility of the Main Request and the Auxiliary Requests

3.1. The requests filed on 26 July 2021

The Main Request and Auxiliary Requests 0A-12C were filed on 26 July 2021, i. e. one day before the final date for making written submissions or amendments under R. 116 EPC. The opponents have requested not to admit the requests as late-filed.

The Division considers that all of these requests must indeed be considered as late-filed, because the amendments therein in comparison to the previously pending requests do not form a response to any unexpected procedural development.

In comparison to the previously pending Main Request and Auxiliary Requests 1-11, the additional amendments in the present Main Request and Auxiliary Requests 1-11 attempt to overcome an objection of lack of novelty over D1 by amending the lower limit value for parameter p, objections of lack of novelty over D2 and D6 by introducing disclaimers, and objections of lack of novelty over D6 and D7 by limiting the employed drug to a cytotoxic drug. In order to avoid a lack of consistency of the claims after the last-named limitation, references to certain non-cytotoxic drugs were cancelled from

dependent claims. Furthermore, the definitions for R_1 - R_4 have been further amended in order to address an objection of lack of novelty over D8 and to overcome objections under Art. 123 and 84 EPC against the previous amendments of this passage.

In Auxiliary Request 12, independent claim 4 was cancelled which addresses objections of lack of novelty over D8 and D9.

In the series of Auxiliary Requests 0A, 1A etc. and in the series of Auxiliary Requests 0C, 1C etc., a further redrafting of the definitions for R_1 - R_4 is provided in order to address the issues mentioned above.

In the series of Auxiliary Requests 0B, 1B etc., the definition of the drug in claims 2 and 4 is limited by incorporation of the additional features of claim 5 of the Main Request in order to ensure novelty over D9.

As such, all of these amendments either address novelty objections which were already raised in the notices of opposition and preliminarily confirmed by the Division in the annex to the first summons or try to ensure that passages which must be amended due to such objections comply with Art. 84 and 123 EPC. The Division considers that it would have been possible for the Proprietor to provide these requests at an earlier stage of the proceedings than one month before the oral proceedings, so that the requests are late-filed. The Division thus had to exercise its discretion whether to admit them into the proceedings.

In exercising its discretion, the Division has come to the conclusion that all of the requests should be admitted, because the amendments therein form fair attempts to overcome the cited objections. The Division does not agree with the opponents' argument that the high number of filed requests offended against the need for procedural economy. Rather, the requests concern different combinations of the relatively few amendments which are discussed above; they thus do not unduly increase the number of issues to be assessed. Even if the requests, as stated by the opponents, do not fully address all of the raised objections or give rise to some new issues under Art. 84 or 123 EPC, there remained sufficient time for the opponents and the Division until the oral proceedings to analyze all of these points and react thereto.

The Division has thus decided to admit all of the requests filed on 26 July 2021 into the proceedings.

3.2. The requests filed during the oral proceedings

Auxiliary Requests 8D-8F were filed during the oral proceedings. The opponents have requested not to admit the requests into the proceedings, because they were late-filed and because they did not qualify as prima facie admissible, as they did not overcome previously raised objections or new objections arose.

The requests contain a number of amendments in comparison to the preceding requests which address objections which had been raised at earlier stages of the procedure. For example, the definition of R_5 and R_6 in the independent claims is amended to overcome an objection under Art. 123(2) EPC against the option that these groups are a polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ wherein the lower limit for p is 1.

However, the requests also contain amendments of the second definition of R_1 - R_4 in the independent claims which address an objection under Art. 123(2) EPC which was raised only during the oral proceedings. According to this objection, item (i) of claim 1 of the Main Request implies that each of R_1 - R_4 is one of the indicated groups such as alkylene, whereas the original disclosure only provided the information that the linker as a whole contains these groups. During the oral proceedings, the Division has agreed with this objection. In subsequently filed Auxiliary Request 8D, the second definition of R_1 - R_4 was amended by rephrasing the relevant passage as "...or R_1 , R_2 , R_3 and R_4 are respectively a chain of atoms selected from... and wherein the said atoms in the hydrophilic linker are combined in any chemically relevant ways forming alkylene...", thus adding the specification that the atoms are present in the hydrophilic linker. In the independent claims of Auxiliary Request 8E, the same amendment was performed and the phrases according to which R_1 - R_4 "are respectively a chain of atoms selected from C, N, O, S, Si and P" and said atoms in the hydrophilic linker are combined "in any chemically relevant ways" were cancelled. In Auxiliary Request 8F, the second definition of R_1 - R_4 has been cancelled as a whole.

In the Division's view, it was necessary to give the Proprietor an opportunity to react to this new objection during the oral proceedings. Auxiliary Requests 8D-8F represent three clearly distinguishable attempts to address the objection and in this respect form appropriate reactions of the Proprietor. This applies irrespective of the circumstance that the requests additionally also address previously raised objections. The Division has thus come to the conclusion that these three requests should not be regarded as late-filed and that it did not have any discretionary power not to admit them.

The Division has thus decided to admit Auxiliary Requests 8D-8F into the proceedings.

4. Admissibility of Documents

4.1. Document D26

It was disputed between the parties whether the proteins in the conjugates of D10 qualify as cell binding agents in the sense of the opposed patent. On 15 July 2020, Opponent 2 has filed D26 which states that T-cell superantigens which are listed as proteins on p. 25, par. 1 of D10 bind to T-cells. The Proprietor has stated that it was not clear why the document would be relevant and has requested not to admit it.

The Division does not agree that the document is late-filed. Opponent 2 had stated in its notice of opposition that T-cell superantigens were cell-binding proteins. This was denied in the Proprietor's reply to the notices of opposition, and the Division had stated in the annex to the first summons of 2 March 2020 that it did not consider it credibly demonstrated that these proteins can act as cell-binding agents. The Division considers that the opponent did not have to expect that its allegation in this respect would be contested, so that the filing of D26 on 15 July 2020 forms a legitimate and timely response to the arguments in the Proprietor's reply to the notices of opposition and the Division's opinion in the annex to the first summons. The Division thus considers that it did not have any discretionary power as to admitting the document. The Division has thus decided to admit D26 into the proceedings.

4.2. Document D28

Document D28 was filed by Opponent 1 on 12 August 2020. A new novelty objection was based on this document. According to the opponent, a replacement of a functional group in the structural formula in par. 45 by a group which is indicated as an alternative in the same paragraph leads to a compound and a conjugate falling within claims 2 and 4 of the then pending Main Request; this compound and this conjugate were implicitly disclosed in D28. The Proprietor has stated that the document was late-filed and that it was not relevant.

The Division considers that the document is late-filed, so that it had to exercise its discretion whether to admit it. In view of the fact that indeed all components of a compound and a conjugate according to claims 2 and 4 are disclosed in D28, the Division is of the opinion that the document is *prima facie* relevant. The Division has thus decided to admit D28 into the proceedings.

5. The Main Request

5.1. Art. 123(2) EPC

5.1.1. *The definition of parameter p in claims 1-4*

According to claims 1-4 as granted, each of R₁-R₆ can be a polyethyleneoxy unit of formula (OCH₂CH₂)_p wherein p is an integer of 0 to 1000. In the Main Request, the range of values for p was amended to from 1 to 1000. The opponents argue that a

violation of Art. 123(2) EPC was given, because the lower limit value of 1 is originally disclosed only for the limited range of 1 to 100 in the context of a much smaller list of selection possibilities for R_1 - R_4 (see p. 12, I. 22-23 of the original application). An inadmissible intermediate generalisation was present in that one to three groups of R_1 - R_4 could now be a polyethyleneoxy unit with $p = 1$ without the limitation of the other R_1 - R_4 groups to the mentioned smaller list of selection possibilities. The standards for compliance with Art. 123(2) EPC according to the "gold standard" as referred to in G 2/10 were not met.

In the Division's view, it follows from the characterisation of the embodiments on p. 12, I. 22-23 of the original application as preferred that, in principle, the combination of the preferred narrow range for p of 1 to 100 with one of the part ranges of the general range of 0 to 1000 which lies on the side of the narrow range is allowable for R_1 - R_4 .

Furthermore, the Division considers that the skilled person had to understand the range for p of 1 to 100 as forming a preferred embodiment for polyethyleneoxy units R_1 - R_4 in general, irrespective of the fact that it is disclosed on p. 12, I. 22-23 in the context of a shorter list of selection possibilities for these groups. The Division thus considers that the skilled person could derive the present definition of R_1 - R_4 as a whole directly and unambiguously from the original documents, so that the requirements defined in the jurisprudence such as in G 2/10 are met. If one regards the amendment as an intermediate generalisation, it is in the Division's view an allowable one.

On the other hand, the lower limit value of 1 for p is originally disclosed on p. 12, I. 22-23 only for groups R_1 - R_4 , but not for groups R_5 and R_6 . The Proprietor has argued that already the reference to a polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ with p being from 0 to 1000 in the original disclosure meant that a polyethyleneoxy unit could be present or absent which in turn implied that p could be 1. In the Division's view, it is correct that the possible presence of such a unit is implicitly disclosed; however, in the absence of a specific reference to p being 1, the presence of a unit of precisely this size as a lower limit cannot be directly and unambiguously derived. Furthermore, in view of the reference in the passage on p. 12, I. 22-23 to R_1 - R_4 only, the Division also cannot agree with the Proprietor that the skilled person would understand the teaching of this passage to also apply to R_5 and R_6 .

The Division is thus of the opinion that the definition of p in the independent claims of the Main Request is not allowable for groups R_5 and R_6 .

5.1.2. *The second definition of R_1 - R_4 in claims 1-4*

Each of claims 1-4 contains two definitions for R_1 - R_4 ; the second definition specifies the moieties which are formed by R_1 - R_4 if these groups are respectively a chain of atoms selected from C, N, O, S, Si and P. According to option (i) of this first definition, "the said

atoms are combined in any chemically relevant ways forming alkylene,... or combinations thereof"; the Division is of the opinion that the reference to "the said atoms" must be understood to refer to the chain of atoms mentioned before. According to option (ii), R_1 - R_4 "are composed of one or more linker components of 6-maleimidocaproyl (MC),...". The opponents consider the definitions in both options as not complying with Art. 123(2) EPC.

According to the original application, the preferred formula for the disclosed cell-binding molecule-hydrophilic linker-drug conjugates is $Cb(-L-Drug)_n$ with L being a hydrophilic linker (see, e. g., p. 3, l. 18-20 and p. 13, l. 8-10). In the embodiment according to formula II (see, e. g., p. 4, l. 25 - p. 5, l. 6 and p. 14, l. 11 - p. 15, l. 2), the part of the conjugate between the moieties Cb and Drug, and thus the hydrophilic linker, is specified as containing groups Q, T and R_1 - R_6 . It is thus clear that R_1 - R_4 form part of the hydrophilic linker.

The most general definition of R_1 - R_4 in the original disclosure is provided, for example, in claim 1 and on p. 4, l. 10-22. These passages also contain the statement that "the atoms used in forming the hydrophilic linker may be combined in all chemically relevant ways, such as forming alkylene...". In the Proprietor's view, this disclosure provides a basis for the drafting of option (i) in the second definition of R_1 - R_4 in the present claims. However, in the Division's opinion, it is only derivable from the original disclosure that, on one hand, R_1 - R_4 are parts of the hydrophilic linker and that, on the other hand, the hydrophilic linker can contain groups such as alkylene, but not that R_1 - R_4 individually would exactly correspond to these groups. The opponents are correct in pointing out that it would also be conceivable that, for example, some of R_2 - R_4 in combination form one of the indicated groups. The skilled person also would rather not consider the list of groups such as alkylene on p. 4, l. 17-22 of the original description as selection possibilities specifically for R_1 - R_4 for the reason that the first definition for R_1 - R_4 in the preceding passage on p. 4, l. 10-14 already covers similar, albeit more specifically defined, groups, such as "linear alkyl having from 1-6 carbon atoms". The definition in option (i) in the second definition of R_1 - R_4 in the Main Request according to which "the said atoms", i. e. the atoms of the chain of atoms making up each of R_1 - R_4 , are combined to form one of the indicated groups is thus not supported by the original disclosure.

The "linker components" according to option (ii) of the second definition of R_1 - R_4 in the Main Request are disclosed as such on p. 13, l. 12 - p. 14, l. 10 of the original application. However, also in this case, it is in the Division's view not possible to consider these components as being originally disclosed as selection possibilities specifically for each of the groups R_1 - R_4 . Also in this case, it seems possible that some of R_1 - R_4 in combination form such "linker components"; furthermore, parts of the shown

"linker components" may rather correspond to the linkage-enabling groups Y and Z in the linker precursor compounds of formula (I) (see p. 3, l. 26 - p. 4, l. 24 of the original application) than to groups R₁-R₄.

The Division thus considers that the drafting of the second definition of R₁-R₄ is not allowable under Art. 123(2) EPC.

5.1.3. *The term "administerable" in claim 16*

Original claim 20 refers to a "pharmaceutical composition comprising a therapeutically effective amount of the immunoconjugate of claim 2 or 13, administered concurrently with the other therapeutic agents such as... or the other immunoconjugates for synergistically effective treatment or prevention of a cancer...". In corresponding present claim 16, the term "administered" has been substituted by the wording "wherein the composition is administerable". Opponent 1 considers that this implies a cancellation of the requirement of a cocurrent administration with another therapeutic agent. The claim now related to a pharmaceutical composition of the conjugate for synergistically effective treatment or prevention of the indicated conditions regardless of the presence of any of the recited further therapeutic agents. Such a synergistically effective treatment or prevention of these conditions was not disclosed in the specification as filed, so that an objection under Art. 123(2) EPC arose.

The Division considers that the skilled person could only interpret the reference to a synergistically effective treatment or prevention as relating to a synergistic effect of the combination of the conjugate and the other therapeutic agent. The Division does not share the Opponent's view that present claim 20 would relate to a synergistically effective treatment or prevention with a composition which does not comprise any of the recited other therapeutic agents. It seems that the only effect of the amendment was to change a feature defining an activity - the concurrent administration itself - into a corresponding feature defining an entity - the ability of the composition for this administration. Furthermore, the indication that a composition is administered under specific conditions allows the direct conclusion that it must be administerable under these conditions to start with, so that no technical information has been added.

The Division thus considers the amendment to comply with Art. 123(2) EPC.

5.1.4. *The disclaimers in claim 1*

Claim 1 contains disclaimers which are directed to comp. 14 and 15 of D6 and comp. 2 of D7.

According to headnote 2.1 of G 1/03, a disclaimer may be allowable in order to restore novelty by delimiting a claim against an accidental anticipation under Art. 54(2) EPC, wherein an anticipation is accidental if it is so unrelated to and remote from the claimed

invention that the person skilled in the art would never have taken it into consideration when making the invention. It is disputed between the parties whether this requirement is presently met.

Comp. 15 of D6 is used as a linker between a fluorescent agent, biotin and a protein; comp. 14 of D6 is its synthetic precursor. Comp. 2 of D7 is presented as a molecule for bioconjugation, in particular for attaching tags to proteins. The Proprietor has pointed out that D6 and D7 do not refer to therapeutic uses like the conjugates according to the opposed patent, but merely to the coupling of biomolecules for different purposes and thus formed accidental anticipations. The Division does believe that a skilled person trying to prepare new therapeutically active compounds would not take into account disclosures wherein no such activity is described. On the other hand, the Division is of the opinion that the situation is different when the skilled person is trying to provide new linkers for molecules of known activities, such as in the field of the opposed patent. In this case, the interesting properties of the potential candidate compounds reside in their ability to link biologically active molecules, and documents which demonstrate such an ability cannot be regarded as being so unrelated that the skilled person would never have taken them into consideration.

The Division has thus come to the conclusion that D6 and D7 do not form accidental anticipations in the sense of G 1/03. This has the consequence that the introduction of the disclaimers in claim 1 is not allowable under Art. 123(2) EPC.

5.1.5. *Summary*

The Main Request does not meet the requirements of Art. 123(2) EPC.

5.2. Art. 84 EPC

In the conjugate according to claim 2 and the compound according to claim 4 of the Main Request, the drug has been specified to be a cytotoxic drug. Opponent 1 considers that, although anti-autoimmune disease agents have been cancelled from dependent claim 5, this claim still encompasses numerous agents which do not qualify as cytotoxic drugs, in particular antiviral drugs (see item 3 of claim 5), so that there is an inconsistency which renders the claims unclear.

Cytotoxic drugs and antiviral drugs form two widely defined classes of drugs of different principles of operation. The Division considers that it can practically be excluded that all of the numerous antiviral drugs which are indicated in claim 5 show also cytotoxic activity. The Proprietor has stated that the opposed patent itself disclosed all of the drugs according to claim 5 as cytotoxic. However, the Division comes to a different conclusion as to the disclosure of the opposed patent. According to par. 79, the patent concerns conjugates of "small molecule drugs including cytotoxic agents", i. e. small molecule drugs in general and cytotoxic agents in particular. Numerous agents which

are listed in present claim 5, including the antiviral agents, are cited in the original disclosure as suitable drugs without any indication that they would be cytotoxic. The Division thus agrees with Opponent 1 that there is an inconsistency between claims 2 and 4 on one hand and claim 5 on the other hand, so that the claims are unclear.

The Division thus considers that the subject-matter of the Main Request does not meet the requirements of Art. 84 EPC.

6. Auxiliary Requests 0A-8C

6.1. Art. 123(2) EPC

Independent claims of each of Auxiliary Requests 0A-8C contain the feature that R_5 and R_6 can be a polyethyleneoxy unit of formula $(OCH_2CH_2)_p$ wherein the lower limit for p is 1 (in combination with an upper limit for p of either 100 or 1000). The objection under Art. 123(2) EPC against this feature which is discussed above with respect to the Main Request thus applies equally against each of these requests.

The Division concludes that the subject-matter of Auxiliary Requests 0A-8C does not meet the requirements of Art. 123(2) EPC.

7. Auxiliary Request 8D

7.1. Art. 123(2) EPC

In the second definition of R_1 - R_4 in the independent claims of Auxiliary Request 8D, item (ii) has been cancelled, and item (i) has been reworded by stating that these groups "are respectively a chain of atoms selected from C, N, O, S, Si, and P that covalently connects the cell-surface binding ligand, the phosphinate or sulfonyl group, the conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), and wherein the atoms in the hydrophilic linker are combined in any chemically relevant ways forming alkylene,... or combinations thereof". Compared to the corresponding wording in the Main Request, it was thus added that the atoms which are combined to form the indicated groups are "in the hydrophilic linker".

In the Proprietor's view, this amendment clarifies that the indicated groups such as alkylene are not selection possibilities for each of R_1 - R_4 as such, but parts of the hydrophilic linker, as originally disclosed in, for example, original claim 1 and on p. 4, l. 17-22 of the original description. However, the Division considers that the amendment does not overcome the objection which applies against the corresponding passage of the Main Request. In the phrase " R_1 , R_2 , R_3 and R_4 are respectively a chain of atoms... and wherein the said atoms in the hydrophilic linker are combined in any chemically

relevant ways forming alkylene...", the wording "the said atoms" must still be understood to refer to the atoms in the chain of atoms which forms each single one of R_1 - R_4 . As in the Main Request, the claims thus define each of R_1 - R_4 by means of groups which are originally disclosed only as constituents of the linker as a whole.

The Division thus considers that the subject-matter of Auxiliary Request 8D does not meet the requirements of Art. 123(2) EPC.

8. Auxiliary Request 8E

8.1. Art. 123(3) EPC

According to the second definition of R_1 - R_4 in the independent claims of Auxiliary Request 8E, " R_1 , R_2 , R_3 and R_4 covalently connect the cell-surface binding ligand, the phosphinate or sulfonyl group, the conjugated drug and among themselves (R_1 , R_2 , R_3 and R_4), and wherein the said atoms in the hydrophilic linker are combined forming alkylene,... or combinations thereof". Compared to Auxiliary Request 8D, the passages were cancelled according to which groups R_1 - R_4 are respectively a chain of atoms selected from C, N, O, S, Si and P and the atoms in the hydrophilic linker are combined in any chemically relevant ways.

In the Division's view, the opponents' assessment that the cancellation of the selection possibilities for the atoms in the chain of atoms leads to a violation of Art. 123(3) EPC is correct. The Proprietor is of the opinion that the cancelled passage was completely superseded by the following more precise definitions of R_1 - R_4 . However, the Division notes that these following definitions leave open the possibility that other than the originally indicated atoms may be present. For example, a divalent group which contains an atom different from C, N, O, S, Si and P may still fall within the definition of an ester or amide. Consequently, the cancellation of the selection possibilities for the atoms has led to an extension of the scope of protection.

The Division thus considers that the subject-matter of Auxiliary Request 8E does not meet the requirements of Art. 123(3) EPC.

9. Auxiliary Request 8F

In independent claims 1-4 of Auxiliary Request 8F, group Y is defined more narrowly than in the Main Request.

Different definitions are provided for R₁-R₄ on one hand and R₅ and R₆ on the other hand in independent claims 1-4. For R₁-R₄, it is indicated that they can be a polyethyleneoxy unit of formula (OCH₂CH₂)_p wherein p is from 1 to 1000; R₅ and R₆ can be such a unit wherein p is from 0 to 1000. Furthermore, the second definition of R₁-R₄ has been cancelled from the independent claims.

In independent claims 2 and 4, the cytotoxic drug has been defined by incorporating the list of chemotherapeutic agents from item 1 of dependent claim 5 according to the Main Request, thus removing the references to other kinds of agents such as antiviral drugs.

9.1. Art. 123 EPC

In the Division's view, all of the objections under Art. 123(2) and (3) EPC which apply against higher-ranking requests are overcome with the cited amendments. The Division thus considers that the subject-matter of Auxiliary Request 8F meets the requirements of Art. 123 EPC.

9.2. Art. 84 EPC

The Division is of the opinion that the discussed objections under Art. 84 EPC which apply against preceding requests are overcome with the cited amendments.

However, in the Division's view, the opponents are correct in pointing out that there is an inconsistency between the limited definition of the drug to a chemotherapeutic agent in claims 2 and 4 on one hand and the indication in claim 9 of the clean version of the claim set (corresponding to claim 11 of the marked-up version) that the immunoconjugate can be used for the treatment of conditions such as an autoimmune disease and the indication in claim 10 of the clean version of the claim set (corresponding to claim 12 of the marked-up version) that the drug can be, for example, a radioactive isotope on the other hand.

The Division thus considers that the subject-matter of Auxiliary Request 8F does not meet the requirements of Art. 84 EPC.

9.3. Art. 83 EPC

9.3.1. With respect to claims 1-4 as granted, Opponent 1 has stated that the patent did not enable the skilled person to carry out what is claimed over the whole claim scope. The definitions of all of R₁-R₆, Y and Z were very broad. In the examples of the opposed patent, only few moieties were used for each of these groups. There was also no example provided for cases wherein one of the further groups Q and T is a sulfoxide group. The figures showed further specific embodiments, but the scope of these embodiments remained limited compared to the claim scope, their preparation was not described sufficiently, and it was not substantiated that they were useful. In this

situation, an undue amount of experimentation was required by the skilled person to realize the claimed invention across the scope of the claims. Opponent 1 has maintained this objection against the subject-matter of Auxiliary Request 8F.

According to the jurisprudence, sufficiency of disclosure indeed presupposes that the skilled person is able to obtain substantially all embodiments falling within the ambit of the claims (see Case Law of the Boards of Appeal of the EPO, 9th ed. 2019, section II.C.5.4). However, as pointed out by the Proprietor, the burden of proof of insufficiency is as a general rule on the Opponent (see Case Law of the Boards of Appeal of the EPO, 9th ed. 2019, section III.G.5.1.2.c)). The Division considers that, for the following reasons, the Opponent's arguments do not suffice to render credible that significant areas of the claimed subject-matter cannot be put into practice.

Claims 1, 2 and 4 of Auxiliary Request 8F refer to a hydrophilic linker; it must be assumed that the functional feature of the hydrophilicity is primarily to be achieved by the presence of the at least one group Q or T which is selected from the polar groups -P(=O)(OM)-, -S(O₂)- and -S(O)-. The generic definitions which are provided for the groups R₁-R₄ which are connecting these groups to each other and to the end groups are significantly limited in comparison to the Main Request. In any case, the respective group does not have to meet any further requirement than merely connecting the indicated moieties while maintaining a hydrophilic overall character of the linker, and the Division does not doubt that the skilled person would be able to design and synthesize linkers with a large variety of such groups. Analogous considerations apply for R₅ and R₆ which are substituents on R₄. The Division also does not doubt that linkers wherein Q or T are -S(O)- can be prepared, even if no example is provided therefor in the opposed patent, and that they can be hydrophilic in view of the polar nature of this group. Independent claim 3 differs from claims 1, 2 and 4 in that it does not refer to the hydrophilicity of the linker, so that this functional feature cannot pose a problem as regards sufficiency of disclosure; furthermore, also in this case, the Division is convinced that the skilled person would be enabled to provide compounds over substantially the whole scope of the definitions of groups Q, T and R₁-R₆.

The definitions for groups Y and Z have been limited to lists of specific functional groups in claim 1; however, claim 3 still generally refers to a group Z which is a functional group that enables reaction with a cytotoxic drug, and claim 4 still generally refers to a group Y which is a functional group that enables reaction with a cell-binding agent. These are broad functional definitions; however, there are no substantiated doubts that the skilled person would be able to employ for each of these groups a range of functional groups including those which are indicated for this purpose in par. 34 and 35 of the description; in principle, the respective group must merely be suitable to produce a linkage.

9.3.2. Opponent 2 has pointed out that, according to each of claims 1-4, all of R_1 - R_6 can be H. However, as the structural formulae in these claims required that R_1 - R_4 are divalent, these groups could in fact not be H. It was thus impossible to practice the invention over the whole scope of the claims.

It seems to be correct that, contrary to R_5 and R_6 , R_1 - R_4 can indeed not be H in compounds according to claims 1-4. However, in the Division's view, this inconsistency has the consequence that the claim also cannot be interpreted to encompass embodiments wherein R_1 - R_4 is H; rather, the skilled person would immediately recognize this indication as erroneous. There is thus in fact no area defined wherein the skilled person might intend to put the invention into practice, but could not do so. Hence, a lack of sufficient disclosure is not present.

9.3.3. Opponent 2 has further referred to the requirement according to claims 1, 2 and 4 that the linker is hydrophilic. The term "hydrophilic" being relative and no definition being given in the opposed patent, the skilled person had to resort to trial and error in identifying sufficiently hydrophilic compounds within the infinite number of compounds covered by the structural definitions in the claims and was thus faced with an undue burden.

As pointed out in T 544/12 which was also cited by both opponents, a definition of a group of compounds in a claim by both structural and functional features is generally acceptable under Art. 83 EPC as long as the skilled person is able to identify, without undue burden, those compounds out of the host of compounds defined by the structural features in the claim which also fulfil the claimed functional requirements. In the Division's view, this requirement is presently met. As already pointed out above, it is credible that hydrophilicity of a linker can in principle be achieved due to the presence of at least one of the polar groups $-P(=O)(OM)-$, $-S(O_2)-$ and $-S(O)-$. It seems that only such embodiments would not fall within the claim scope wherein firstly other moieties are selected to be hydrophobic and wherein secondly this property would be so predominant that the linker as a whole could not be regarded as hydrophilic anymore, but would take on hydrophobic character as a whole. If at all, an uncertainty could then only arise in a limited area at the boundaries of the claims. Furthermore, the hydrophilic or hydrophobic character of different moieties is generally known; for example, as pointed out by Opponent 2, long-chain alkyl groups are known to be generally hydrophobic. The skilled person would thus be able to provide a large variety of embodiments of the claimed subject-matter which doubtless fall within the claim scope, and it could not be held that it was deprived of the possibility to implement the claimed teaching over substantially the whole claim scope.

With respect to the statement of Opponent 2 that the skilled person was confronted with the undue burden of identifying compounds which are sufficiently hydrophilic to provide the advantages alleged for the invention, it is pointed out that Art. 83 EPC requires merely that the teaching of the claims as such can be realized, i. e. in the present case that a hydrophilic linker of the indicated structure can be provided. A certain minimum degree of hydrophilicity may be necessary to achieve certain effects which could be of relevance in the assessment of inventive step, but does not have to be present to meet the requirement of a sufficient disclosure for present claims 1-4.

9.3.4. The Division thus considers that the subject-matter of Auxiliary Request 8F meets the requirements of Art. 83 EPC.

9.4. Art. 54 EPC

9.4.1. *Claim 2 - Novelty over D1*

Comp. 2 of D1 (see Fig. 1) is a conjugate wherein, in the terminology of present claim 2, m is 1 and n is 0, the sulfoxide group forms a group Q, and the adjacent ethylene group forms a group -R₂-R₄(R₅)(R₆)-. The groups which are attached at the ends of the linker are an antibody which is a cell-binding agent and a maytansinoid which is a drug. As the succinimidyl group adjacent to the sulfoxide group comprises an amide group and further amide groups are present connecting the discussed parts of the linker with the drug and the cell-binding agent, also the requirement in claim 2 that the drug is linked to the cell-binding agent via the hydrophilic linker by one of a list of specific bonds such as an amide bond is met.

The Proprietor considers that comp. 2 of D1 does not contain a group R₁ as defined in present claim 2. However, the claim states that R₁ can be "1-6 carbon atoms of esters, ether, amide". In the Division's view, this wording merely requires that an ester, ether or amide group which contains 1-6 carbon atoms is present; unlike terms such as "alkyl", the terms "ester", "ether" and "amide" are generally not understood to exclude the presence of substituents. Consequently, the succinimidyl group which in comp. 2 of D1 is adjacent to the sulfoxide qualifies as a group R₁.

In the Proprietor's view, it further had to be understood that, in comp. 2 of D1, the drug was DM1 the structure of which is shown in the Wikipedia article D30. This drug contains a thiol group. The sulfoxide group at the corresponding position of comp. 2 was thus part of the drug and could not qualify as group Q or T of the linker. This was confirmed by the generic structural formulae in claim 1 and par. 5 of D1 which showed that the group -X(=O)- which corresponds to the sulfoxide group of comp. 2 was adjacent to the cytotoxic agent D. The Division does not agree. Present claim 2 allows the drug to be not only DM1 in particular, but any maytansinoid in general and also explicitly refers to synthetic analogs of maytansinoids (see item b) of the list of

chemotherapeutic agents). The Division is convinced that, if the linker is interpreted as discussed above, the remaining part of comp. 2 of D1 which corresponds to group D according to present claim 2 and which includes the ring system remains unambiguously identifiable as a maytansinoid or at least a synthetic analog thereof. The subject-matter of present claim 2 is thus anticipated by D1.

9.4.2. Claim 2 - Novelty over D8

D8 discloses the compounds Herceptin-PEG-PG-TXL and C225-PEG-PG-Adr (see p. 19 and Fig. 2) which contain an antibody cell-binding agent and, as a drug, paclitaxel (TXL) or doxorubicin (Adr) both of which are listed in present claim 2 (see item b) of the list of chemotherapeutic agents). In the linker, m is 1 and n is 0, an ethylene group forms R₁ and a sulfonyl group forms Q. A PEG group which is derived from vinylsulfonyl N-hydroxysuccinimidyl PEG of a molecular weight of 3400 (see p. 15, l. 12-13) qualifies as a group R₂; this group is further bonded to a polyglutamate group wherein the glutamic acid residues carry the drugs.

In the Division's opinion, the first glutamate moiety in each of these compounds qualifies as a combination of an amine and an ester moiety as they are indicated in present claim 2 as selection possibilities for R₄. As pointed out in the discussion of novelty over D1, the Division does not consider that the terms "1-6 carbon atoms of esters, ether, amide,... or combination thereof" exclude the presence of substituents. Consequently, the presence of a polyglutamate residue carrying multiple drug moieties does fall within the definition of the group -R₄(R₅)(R₆)-. The subject-matter of claim 2 is thus anticipated by D8.

9.4.3. Claim 2 - Novelty over D9

Comp. 5b of D9 (see Fig. 2 on p. 1387) contains a human serum albumin (HSA) moiety which carries four MMAE groups and five chains carrying a cell-binding RGD peptide. The chains correspond to formula (II) as defined in claim 2, wherein m is 1 and n is 0, R₁ is ethylene, Q is sulfonyl and R₂ and -R₄(R₅)(R₆)- are both PEG.

MMAE is an auristatin, and auristatins are listed as drugs in present claim 2 (see item b) of the list of chemotherapeutic agents). The Proprietor states that only MMAE itself could be regarded as a cytotoxic drug, but not the MMAE-carrying HSA as a whole. The HSA was merely a carrier to which the drug was bound via a linker. However, in the Division's view, the term "auristatins" as used in claim 2 must be interpreted to encompass entities which contain auristatin units as long as these entities as a whole retain the pharmaceutical activity. This is confirmed by the statement in par. 79 of the opposed patent according to which the discussed cytotoxic agents can be modified for linkage to the cell-binding agent; a bonding onto HSA can be regarded as such a modification. Against this background, the Division concludes that the auristatin-carrying

HSA of D9 qualifies as an "auristatin" in the sense of claim 2. The Proprietor has also pointed out that comp. 5b of D9 contains five chains of the linker and the cell-binding peptide; however, in view of the above, some of these chains can also be considered as forming part of the "auristatin", so that no differentiating feature is given in this respect. The subject-matter of claim 2 is thus anticipated by D9.

9.4.4. Claim 3 - Novelty over D6

In comp. HRP-4 of D6 (see Scheme 4 on p. 4044), a nitrogen atom carrying a fluorophore and an alkynyl group is connected to horseradish peroxidase (HRP) via a linker. If the terminology of present claim 3 is read on this linker, m and n are both 1, R₁ is ethylene, Q and T are both sulfonyl, R₂ is ethylene in combination with a PEG unit (OCH₂CH₂)₂, and each of R₃ and -R₄(R₅)(R₆)- are methylene.

Documents D24 and D25 provide evidence that HRP binds to mammalian cells (see the summary of D24) and to HeLa cells (see the summary of D25). The Proprietor considers that novelty over D6 had to be acknowledged, because it was not demonstrated that, in the conjugate HRP-4, HRP maintains this cell-binding activity. It is correct that D6 itself only demonstrates an enzymatic activity of the prepared conjugates (see the section "3. Functionality of the Labeled HRPs and the Biotin Tag" on p. 4042-4043). However, in the Division's view, it is not a realistic assumption that the single modification of HRP which leads to comp. HRP-4 could lead to a complete loss of all of the cell-binding activities of the enzyme.

As is demonstrated by the reaction to HRP-11 in Scheme 4 of D6, the alkynyl group can be linked with a compound with an azide group under formation of a triazole; the ability to enable linkage of a cytotoxic drug via a heteroaromatic bond as required for group Z by present claim 3 is thus present. The Proprietor is of the opinion that only the ethynyl moiety should be regarded as a group Z, so that the fluorophore-carrying amine group of HRP-4 would have to be considered as part of the linker wherein it would not fall within the scope of the definition of R₄. However, in the Division's view, the definition of group Z in claim 3 as a functional group that enables linkage of a cytotoxic drug via certain kinds of bonds is so broad that also the whole moiety of HRP-4 which comprises the nitrogen atom, the fluorophore and the alkynyl group falls within its scope, so that the nitrogen atom does not have to be regarded as part of R₄ and, as stated above, the latter can be considered to be constituted just by a methylene group. The subject-matter of claim 3 is thus anticipated by D6.

9.4.5. Claim 3 - Novelty over D7

In comp. 16 of D7 (see Scheme 2 on p. 669), bovine serum albumin (BSA) is bonded to ferrocene via a linker. The linker is a linker in the sense of present claim 3 wherein m is 1 and n is 0, R₁ is ethylene, Q is sulfonyl and R₂ and -R₄(R₅)(R₆)- are both methylene

(see also the structure of the precursor compound 11 in Scheme 1 on p. 668 of D7). D23 shows that BSA binds on tumor cells (see the abstract). The opponents have credibly argued that the ferrocenyl group allows the linkage of a cytotoxic drug via bonds as indicated in the definition of Z in present claim 3, for example by forming an amine in a Mannich reaction. The Proprietor has pointed out that there was no evidence that BSA maintains its cell-binding activity after having been modified to comp. 16 and that also the further reactions in order to establish the linkage of the cytotoxic drug could destroy this activity by denaturing the protein. However, in the Division's view, it can practically be excluded that the single modification of BSA which provides comp. 16 would lead to a complete loss of its cell-binding activity, and there are also no reasons to doubt that a reaction of the ferrocenyl group to introduce a cytotoxic drug can be performed under conditions which are sufficiently mild that this cell-binding activity is at least partially maintained. The subject-matter of claim 3 is thus anticipated by D7.

9.4.6. Summary

The Division concludes that the subject-matter of Auxiliary Request 8F lacks novelty over D1, D6, D7, D8 and D9.

10. Auxiliary Requests 9-12C

10.1 Art. 123(2) EPC

Independent claims of each of Auxiliary Requests 9-12C contain the feature that R₅ and R₆ can be a polyethyleneoxy unit of formula (OCH₂CH₂)_p wherein the lower limit for p is 1. The objection under Art. 123(2) EPC against this feature which is discussed above with respect to the Main Request thus applies equally against each of these requests.

The Division concludes that the subject-matter of Auxiliary Requests 9-12C does not meet the requirements of Art. 123(2) EPC.

III. Decision

The opposed patent is revoked because, taking into consideration the amendments made by the Proprietor during the opposition proceedings, the patent and the invention to which it relates do not meet the requirements of the EPC (Art. 101(3)(b) EPC).