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Datasheet for the decision of 5 December 2022

Case Number:	T 0607/20 - 3.3.07
Application Number:	13717212.8
Publication Number:	2833867
IPC:	A61K9/00, A61K47/12, A61K47/18, A61K9/14, A61K9/16, A61K9/20, A61K9/28, A61K9/48, A61K9/50, A61K9/51
Language of the proceedings:	EN

Title of invention:
SOLID ORAL PHARMACEUTICAL COMPOSITIONS FOR ISOXAZOLINE COMPOUNDS

Patent Proprietor:
Intervet International B.V.

Opponents:
VIRBAC

Headword:
Solid Oral Isoxazoline Compositions / INTERVET

Relevant legal provisions:
RPBA 2020 Art. 12(4), 13(1), 13(2)
EPC Art. 83, 56

Keyword:
New items of evidence - admittance of documents filed in appeal proceedings
Amendment to appeal case - suitability of amendment to resolve issues raised (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:
T 0501/94, T 0553/11, T 0491/08

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Case Number: T 0607/20 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 5 December 2022

Appellant: (Opponent 1)	VIRBAC 1ère Avenue, 2065m, L.I.D. 06516 Carros (FR)
Representative:	Lavoix 2, place d'Estienne d'Orves 75441 Paris Cedex 09 (FR)
Respondent: (Patent Proprietor)	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer (NL)
Representative:	Intervet International B.V. Hertford Road Hoddesdon, Hertfordshire EN11 9BU (GB)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 3 January 2020 concerning maintenance of the European Patent No. 2833867 in amended form.**

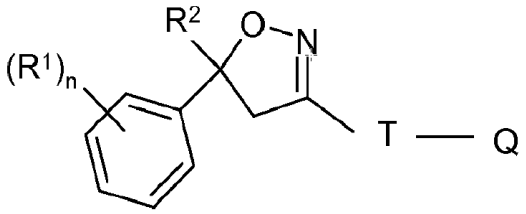
Composition of the Board:

Chairman	A. Usuelli
Members:	J. Lécaillon
	A. Jimenez

Summary of Facts and Submissions

I. European patent EP 2 833 867 (hereinafter "the patent") was granted on the basis of 16 claims. The independent claims of the patent as granted read as follows:

"1. A soft chewable veterinary pharmaceutical composition for oral administration comprising an isoxazoline compound of Formula (I)

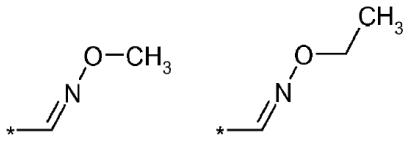


Formula (I),

wherein

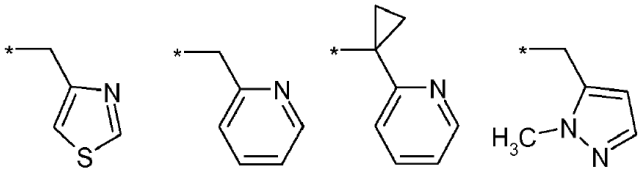
R^1 = halogen, CF_3, OCF_3, CN,
n = integer from 0 to 3, preferably 1, 2 or 3,
R^2 = C_1-C_3-haloalkyl, preferably CF_3 or CF_2Cl,
T = 5- or 6-membered ring, which is optionally substituted by one or more radicals Y,
Y = methyl, halomethyl, halogen, CN, NO_2, NH_2-C=S, or two adjacent radicals Y form together a chain, especially a three or four membered chain;
Q = X-NR^3R^4 or a 5-membered N-heteroaryl ring, which is optionally substituted by one or more radicals;
X = CH_2, $CH(CH_3)$, CH(CN), CO, CS,
R^3 = hydrogen, methyl, haloethyl, halopropyl, halobutyl, methoxymethyl, methoxyethyl, halomethoxymethyl, ethoxymethyl, haloethoxymethyl, propoxymethyl, ethylaminocarbonylmethyl, ethylaminocarbonylethyl, dimethoxyethyl,

propynylaminocarbonylmethyl, N-phenyl-N-methylamino, haloethylaminocarbonylmethyl, haloethylaminocarbonylethyl, tetrahydrofuryl, methylaminocarbonylmethyl, (N,N-dimethylamino)-carbonylmethyl, propylaminocarbonylmethyl, cyclopropylaminocarbonylmethyl, propenylaminocarbonylmethyl, haloethylaminocarbonylcyclopropyl,

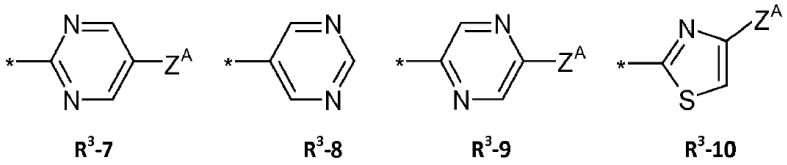


R^3-1

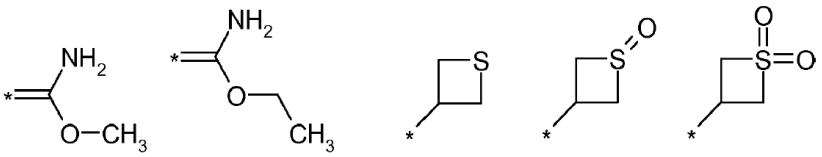
R^3-2



R^3-3 R^3-4 R^3-5 R^3-6



R^3-7 R^3-8 R^3-9 R^3-10

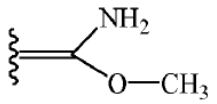


R^3-11 R^3-12 R^3-13 R^3-14 R^3-15

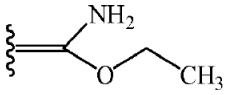
wherein Z^A = hydrogen, halogen, cyano, halomethyl (CF_3);

R^4 = hydrogen, ethyl, methoxymethyl, halomethoxymethyl, ethoxymethyl, haloethoxymethyl, propoxymethyl, methylcarbonyl, ethylcarbonyl, propylcarbonyl, cyclopropylcarbonyl, methoxycarbonyl,

methoxymethylcarbonyl, aminocarbonyl, ethylaminocarbonylmethyl, ethylaminocarbonylethyl, dimethoxyethyl, propynylaminocarbonylmethyl, haloethylaminocarbonylmethyl, cyanomethylaminocarbonylmethyl, or haloethylaminocarbonylethyl;
Or R^3 and R^4 together form a substituent selected from the group consisting of:



and



or a salt or solvate thereof, a solid carrier and a solvent wherein the solvent is selected from 2-pyrrolidone, dimethyl acetamide or mixtures thereof."

"14. A method of preparing the composition of any of claims 1 to 13 comprising dissolving the isoxazoline compound as defined in claim 1, 5, 6, 7, 8, or 9 in the solvent and then adsorbing the resulting solution on to the solid carrier excipient."

"16. Use of the he [*sic*] composition of any of claims 1 to 13 for the manufacture of a medicament for controlling parasite infestation in an animal."

II. Two oppositions were filed against the patent. During the first instance proceedings on 30 August 2019 opponent 2 withdrew its opposition and is no longer party to the proceedings.

III. The opposition division took the decision that, on the basis of the main request, the patent met the requirements of the EPC. The main request was filed with the letter of 2 April 2019. The claims of this main request correspond to the granted claims wherein the dependency of claims 12 and 13 was amended by

deleting the dependency on previous claim 4 (in claim 12) and claim 3 (in claim 13).

IV. The decision of the opposition division, posted on 3 January 2020, cited *inter alia* the following documents:

D1: US 2004/0037869 A1
D6: US 2011/0059988 A1
D7: WO 2008/030469 A2
D8: WO 2011/075591 A1
D13: Chiou *et al.*, J. Pharm. Sci.,Vol. 60, No. 9, 1281-1302 (1971)
D14: Jain *et al.*, Asian J. Pharm. Clin. Res., Vol. 5, Suppl. 4, 15-19 (2012)
D15: Handbook of Pharmaceutical Excipients, Dimethylacetamide, Sixth Ed. (2009)
D16: Handbook of Pharmaceutical Excipients, 2-pyrrolidone, Sixth Ed. (2009)
D21: Friedrich *et al.*, European Journal of Pharmaceutics and Biopharmaceutics, 62, 171-177, (2006)
D25: Michael E. Aulton, "Pharmaceutics, The Science of Dosage Form design", Second Edition, published 2002, "Chapter 17: Bioavailability-physicochemical and dosage form factors", 234-252
D26: Summary Report Study E10-046-100
D27: Summary Report Study E10-046-100 and declaration of Feli Walther

V. The opposition division decided in particular as follows:

(a) The main request fulfilled the requirements of Rule 80 EPC and Articles 123(2) and (3) EPC.

(b) The granted patent as a whole provided sufficient information to prepare a composition according to the claims and achieving improved bioavailability (Article 83 EPC).

(c) The main request fulfilled the requirements of Article 54 EPC.

(d) Document D6 was the closest prior art. The difference between the claimed subject-matter and D6 resided in that the composition was in a soft chewable form and comprised specific solvents. An improved bioavailability had been credibly substantiated to be at least in part due to the presence of these solvents. The problem to be solved was thus the provision of isoxazoline compositions with increased bioavailability. The claimed solution was not obvious in light of the prior art (Article 56 EPC).

VI. Opponent 1 (appellant) lodged an appeal against the above decision of the opposition division.

VII. With its reply to the statement setting out the grounds of appeal the patent proprietor (respondent) defended its case on the basis of the main request filed on 2 April 2019 and maintained during opposition proceedings, and on the basis of auxiliary requests 1, 1a, 1b, 2, 2a, 3, 3a to 3e, 4 to 6 and 6a filed therewith. The content of the claims of the main request is illustrated above (see item III.).

VIII. The following items of evidence were filed by the parties during the appeal proceedings:

(a) Documents filed by the appellant with its statement setting out the grounds of appeal:

D33: Sowmya *et al.*, IRJP, 2012, 3(7), 108-115
D34: Material Safety Data Sheet of Bravecto
D35: Jain *et al.*, International Journal of Pharmaceutics, 342, 2007, 1-5

(b) Documents filed by the respondent with its reply to the statement setting out the grounds of appeal:

D36: CVMP assessment report for Bravecto, EMA, 12 December 2013
D37: "Bioavailability." Merriam Webster.com Dictionary, Merriam-Webster, https://www.merriamwebster.com/dictionary/bioavailability Accessed 28 Sep. 2020

(c) Documents filed by the appellant with the letter of 15 March 2022:

D38: Supplemental experimental results "Fluranaler Formulation"

IX. Oral proceedings were held before the Board on 5 December 2022.

X. The appellant requested that the decision under appeal be set aside and the patent be revoked.

The appellant further requested that:
- documents D36 and D37 not be admitted into the proceedings,
- auxiliary requests 1a, 1b, 2a, 3a to 3e, 4 and 6a not be admitted into the proceedings, and

- the case be remitted to the first instance should the auxiliary requests 1 to 6 filed in first instance be taken into consideration.

XI. The respondent requested that the appeal be dismissed, *i.e.* that the patent be maintained as amended during first instance proceedings (main request filed on 2 April 2019), or that the patent be maintained on the basis of one of auxiliary requests 1, 1a, 1b, 2, 2a, 3, 3a to 3e, 4 to 6 and 6a filed on 2 October 2020 with the reply to the statement setting out the grounds of appeal, wherein auxiliary requests 1, 2, 3, 5 and 6 had already been filed during first instance proceedings on 2 April 2019.

The respondent further requested that:
- documents D33 to D35 and D38 not be admitted into the proceedings, and
- document D36 be admitted into the proceedings should D34 be admitted.

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

(a) D33 to D35 illustrated the common general knowledge and should thus be admitted into the appeal proceedings. Moreover, the respondent bore the burden of proof regarding the lack of public availability of D34 on the date mentioned on it. Furthermore, D35 already formed part of the opposition proceedings because it was cited in D16 (see reference 1 in D16).

(b) D36 and D37 should not be admitted into the appeal proceedings.

(c) D38 should be admitted into the appeal proceedings. In particular, this document was appropriate to resolve the issues on file regarding the achievement of the technical effect over the entire scope of the claims.

(d) The main request did not fulfill the requirements of Article 83 EPC. The skilled person would not have known how to prepare a soft chew composition not containing a forming agent (independent claim 1). Furthermore, the patent did not provide sufficient information regarding how to achieve the improved bioavailability required for the claimed therapeutic use with compositions obtained without pre-dissolution of the active ingredient in the claimed solvent (independent claim 16).

(e) Both D6 and D8 could represent the closest prior art document. Starting from any of these documents, the distinguishing features resided in the nature of the solid dosage form (soft chew) and the presence of a specific solvent (2-pyrrolidone and/or dimethyl acetamide, DMAC). The partial problem approach was to be applied because both distinguishing features and the associated technical effects were functionally independent from each other. Each of the partial problems (as formulated during oral proceedings) resided in the provision of an alternative oral veterinary parasiticide composition and each of the solutions to the partial problems was suggested in the prior art.

During oral proceedings, the appellant further argued that, even if the partial problems approach was not followed, no particular technical effect,

in particular no improved bioavailability, had been substantiated over the entire breadth of the claims. The objective technical problem remained therefore the provision of an alternative. The solution offered in claim 1 would be obvious in view of D6, which provided a pointer to the preparation of soft chew compositions, in combination with D21 or D33. The main request did thus not meet the requirements of Article 56 EPC.

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

(a) D33 to D35 should not be admitted into the appeal proceedings because they could have been filed earlier and did not illustrate common general knowledge. D33 was furthermore not suitable to address the assessment of D21 made in the impugned decision.

(b) D36 was filed in response to D34. It was thus to be admitted into the appeal proceedings if D34 was. D37 should be admitted into the appeal proceedings, because it illustrated the common general knowledge and was filed in direct response to the appellant's objection of lack of sufficiency of disclosure for claim 16.

(c) D38 was not to be admitted into the appeal proceedings because the tests provided therein did not substantiate that the improved bioavailability shown for the claimed compositions was due to pre-dissolution of the active agent in the solvent.

(d) The main request met the requirements of Article 83 EPC. The original application provided sufficient

information for the skilled person to prepare a composition according to the claims and rendered the veterinary use thereof as parasiticide in animals plausible. In particular, the achievement of an improved bioavailability was not required.

(e) The main request fulfilled the requirements of Article 56 EPC. D6 represented the closest prior art document. Starting from D6, the distinguishing features resided in the nature of the solid dosage form (soft chew) and the presence of a specific solvent (2-pyrrolidone and/or DMAC). These distinguishing features and the associated technical effects were functionally interdependent, so that the partial problem approach was not appropriate. An improved bioavailability had been substantiated for the claimed soft chew compositions. The objective technical problem was therefore to be formulated as the provision of a new oral dosage form of the compounds that results in an improved safety and/or efficacy and bioavailability with a desirable pharmacokinetic profile. None of the prior art documents provided any suggestion or motivation to prepare a soft chew composition with the present solvents to solve this problem.

Reasons for the Decision

1. Admittance of items of evidence

1.1 Documents D33 to D37

1.1.1 Documents D33 to D37 were submitted with the statement setting out the grounds of appeal (D33 to D35) or the reply thereto (D36 and D37), both filed after 1 January

2020. The issue of their admittance is to be decided on the basis of Article 12(4) RPBA 2020.

1.1.2 D33 was filed by the appellant in reply to the impugned decision, in which it was considered that methanol was taught as a preferred solvent for the solvent deposition technique (see page 17, 3rd paragraph of the impugned decision).

Despite being a review article, D33 concerns a very specialised technique and was published in a specialist journal. Contrary to the appellant's opinion, D33 does therefore not form part of common general knowledge.

Nevertheless it addresses an issue which contributed to the first instance decision and does not appear to introduce any particular complexity.

During oral proceedings, the respondent argued that D33 was more specific than D21 because it concerned the liquid/solid technique. Besides, according to the abstract of D33, the carrier in D33 would be coated, which technique would not be described in D21. D33 could therefore not address the opinion of the opposition division on D21.

This argument is not convincing. The Board observes that both D21 and D33 generally relate to the technique discussed in the impugned decision, namely drug solution deposition onto absorbents, and the use of various solvents therein. Besides not the carrier *per se* but the final "liquidsolid compacts" are coated in D33, *i.e.* the drug is first absorbed on a non-coated carrier as in D21.

It follows that D33 appears suitable to address the issue raised in the impugned decision (Article 12(4) RPBA 2020). D33 is therefore admitted into the appeal proceedings.

1.1.3 The date of public availability of D34 was disputed by the respondent. The Board observes that the sole date indicated on the document itself corresponds to the "creation date" and the "last revision date". It is doubtful that this date corresponds to the date at which the document was made available to the public. Contrary to the assertion of the appellant, the mention of this date on the document did therefore not discharge the appellant from its burden of proof.

Hence, D34 is not admitted into the appeal proceedings, since its belonging to the relevant state of the art remains doubtful (Article 12(4) RPBA 2020).

1.1.4 Contrary to the opinion of the appellant, the fact that D35 was cited as reference 1 in D16 (referred to as D18 in the statement of grounds of appeal) does not make it automatically part of the proceedings (see T 501/94 Catchword II. and Case Law of the Boards of Appeal, 9th Edition IV.C.4.4, 5th paragraph). Since D35 has not been cited as prior art during the first instance proceedings, it does not already form part of the proceedings.

Furthermore D35 is a scientific article published in a specialised journal and does thus not form part of the common general knowledge.

According to the appellant, this document would confirm the teaching of D16, that 2-pyrrolidone would be a better solubilizing agent than other solvents such as

ethanol. The disclosure of D16 *per se* has however not been disputed in the first instance decision.

It is therefore not apparent in which measure the filing of D35 would be suitable to address any issue which led to the impugned decision (Article 12(4) RPBA 2020). Accordingly, D35 is not admitted into the appeal proceedings.

1.1.5 D36 was filed by the respondent in reaction to the submission of D34, in support of the objection regarding the date of public availability of D34. Since D34 is not admitted into the proceedings, D36 is also not admitted therein (Article 12(4) RPBA 2020).

1.1.6 D37 provides a definition of the term "bioavailability". While the definition of the level of bioavailability required for the claimed therapeutic effect to be credibly achieved differs among the parties, the actual meaning of the term "bioavailability" has not been disputed. The late filing of evidence of common general knowledge of the meaning of this term is thus not required.

It is therefore not apparent in which measure the filing of D37 would be suitable to address any issue which led to the impugned decision (Article 12(4) RPBA 2020). Hence, D37 is not admitted into the appeal proceedings.

1.2 Document D38

1.2.1 The document D38 was submitted on 15 March 2022, *i.e.* after notification of the summons to oral proceedings. The issue of its admittance is to be decided on the basis of Articles 13(1) and 13(2) RPBA 2020.

1.2.2 Independently of the issue of whether there would be exceptional circumstances which may justify the filing of D38 at this stage of the proceedings (Article 13(2) RPBA 2020), the Board considers that D38 is not suitable to resolve the issues on file, contrary to Article 13(1) RPBA 2020, for the reasons detailed below (see 1.2.4 to 1.2.6).

1.2.3 D38 was filed to substantiate that the mere addition of 2-pyrrolidone without prior dissolution of the isoxazoline therein does not achieve the alleged effect, so that an improved bioavailability would thus not be achieved over the whole scope of the claims.

According to the appellant, the test performed in D38 compared under the same experimental conditions one composition according to the claims (composition B) and one strictly comparative control composition, which differed from the first composition only in the absence of 2-pyrrolidone (composition A). There was no requirement in the EPC that comparative test would have to be performed with compositions identical to those already tested or to the ones exemplified in the patent. A comparison with a composition wherein the drug would have been pre-dissolved in 2-pyrroldione was thus not necessary.

Finally the appellant argued that the present *in vitro* tests were a recognised alternative method to *in vivo* tests, which were subject to regulatory agencies' authorisation and not in line with the appellant's company policy regarding the respect of animal well-being.

1.2.4 The Board observes that the experiment performed in D38 is limited to *in vitro* dissolution data over 6 hours. While these data may indeed provide some trend regarding the bioavailability of poorly soluble drugs, they cannot anticipate pharmacokinetic data in the absence of a demonstrated direct correlation between both data. Furthermore D38 concerns two specific compositions which differ from those tested so far (nature and/ or amounts of excipients), so that no pharmacokinetic data are otherwise available for the compositions of D38.

1.2.5 Moreover, the purpose of D38 is to show that the effect alleged by the respondent (increased bioavailability) is fulfilled only when a pre-dissolution is done but not when the claimed solvent is merely added together with all the other components. However, D38 does not provide any comparison with a composition obtained with pre-dissolution, *i.e.* there is no "positive control" in D38. The patent provides data on the improved bioavailability of compositions obtained with pre-dissolution. In the absence of any data in D38 as to the dissolution behaviour of these compositions it cannot be established whether their high bioavailability is due to an increased dissolution rate. In other words, no clear correlation can be made between dissolution and bioavailability. In D38 no significant improvement of the dissolution rate over 6 hours is observed for the composition containing the solvent prepared without pre-dissolution. However, in view of the considerations presented above, this does not necessarily imply that the bioavailability of this composition would not be improved. Furthermore a similar dissolution rate over 6 hours could possibly have been observed also for compositions prepared with a step of pre-dissolution. Thus, the experiments of D38

do not appear to serve the purpose for which they have been made.

1.2.6 Since the effect measured in D38 is not exactly the one alleged by the respondent and in the absence of any evidence of a direct correlation between these two effects as well as of a positive control in D38, it cannot be concluded that the test used in D38 is appropriate to show that the alleged effect is indeed achieved or not.

1.3 Accordingly, D38 is not admitted into the proceedings (Article 13(1) RPBA 2020).

Main request

2. Amendments

The subject-matter claimed in the main request is disclosed in the original claims and the original description. Furthermore the scope of the claims was not broadened compared to the one of the granted claims. The appellant did not raise any objection under Articles 123(2) and 123(3) EPC for the performed amendments. The Board considers that the requirements of Articles 123(2) and 123(3) EPC are fulfilled.

3. Sufficiency of disclosure

3.1 The appellant contested that the product of claim 1 and the use of claim 16 of the main request would be sufficiently disclosed.

3.2 Independent claim 1

3.2.1 Independent product claim 1 is defined by:
- its components (isoxazoline (I), solid carrier,specific solvent), and
- a physical characteristic *i.e.* the composition being a "soft chew".

3.2.2 The patent describes the various components and amounts thereof as well as methods for the preparation of the composition (see paragraphs [0055]-[0060] and examples). The soft chew characteristic is also described (see paragraphs [0061]-[0063]) and one example of preparation of a soft chew composition according to the invention is described in paragraph [0072]. Soft chew formulations and their preparations appear furthermore to be commonly known in the art (see D7, page 11 lines 19-20).

3.2.3 The appellant argued that the patent as well as D26 and D27 only described compositions comprising a forming agent (see paragraph [0062] of the patent and examples according to the invention, which all contain PEG3350 or PEG8000 as forming agent) and that the skilled person would not know how to prepare a soft chew composition not containing any forming agent. Since independent claim 1 also encompassed such compositions, the claim would not be sufficiently disclosed in the patent.

3.2.4 The Board notes that the patent indeed states that a forming agent is "important for the texture" of the soft chew composition (see paragraph [0062]). This forming agent is then described in details (see paragraphs [0062] to [0063]). Hence, the skilled person knows from this passage that a soft chew with an

appropriate texture can be achieved by using a forming agent, which is not excluded from the claims. However the Board considers that this passage does not teach that a forming agent is an essential feature, which should be in the claims. As stated above (see point 3.2.2), the patent provides one way of carrying out the invention, even if it includes a forming agent (PEG 8000). Furthermore, as indicated by the respondent, other processes appear to be available in the art, including the one described in D7 (see page 11) which does not explicitly mention a forming agent, so that the skilled person could apply such alternative processes. Finally, the appellant has not effectively shown that processes without a forming agent do indeed not work.

3.2.5 Even if the forming agent would be essential, its non-inclusion in the claims would in the present case merely be an issue of clarity, since this feature and its role are disclosed in details in the description.

3.2.6 Regarding the decision T 553/11 cited by the appellant, the Board notes that the catchword of this decision states that "Embodiments that are covered by the scope of a claim on its ordinary reading are not to be regarded as excluded merely because it can be deduced from the description that they are not workable". The description of the present patent does not teach that soft chew compositions according to claim 1 are not workable at all without forming agent (see above point 3.2.4). There is therefore no reason to read present claim 1 as if soft chew compositions deprived of any forming agent would be excluded form its scope. The present case differs therefore from the one underlying the decision T 553/11.

3.2.7 Accordingly, the Board comes to the conclusion that, from the teaching of the patent as a whole, the skilled person is able to prepare a composition comprising the components listed in independent claim 1 and being in the form of a soft chew.

3.3 Independent claim 16

3.3.1 Claim 16 relates to the therapeutic use of the claimed composition in controlling parasite infestation in an animal.

3.3.2 It is known from the prior art that isoxazolines of formula (I) have parasiticidal activity (see paragraphs [0002], [0003], [0046] to [0048] and [0051] of the patent) and are effective upon oral administration (see example 9 of the patent and the examples of D6). Since the compositions of claim 1 are oral compositions containing such isoxazolines, the Board considers it plausible that the compositions achieve the claimed therapeutic effect of controlling parasite infestation in an animal.

3.3.3 Hence, contrary to the assertion of the appellant, the Board considers that, in view of the prior art, there is already a high presumption that the claimed therapeutic effect is achieved. Therefore decision T 491/08 (see point 12 of the reasons), cited by the appellant, does not apply to the present case.

3.3.4 According to the appellant an improved bioavailability would be required for the claimed therapeutic effect to be achieved. However, an improved bioavailability would have been substantiated only for compositions obtained with a pre-dissolution of the active agent (see *e.g.* paragraphs [0033] and [0071]-[0072] of the patent),

i.e. the patent would not substantiate that all the claimed compositions would have sufficient bioavailability to achieve the claimed therapeutic use.

3.3.5 Achievement of an improved bioavailability is however not a feature of the claims. The Board does further not recognise how it would constitute a pre-requisite to the claimed therapeutic use. It is an undisputed fact that some bioavailability is indeed required when administering a drug *per* oral route so as to achieve a known therapeutic effect of said drug. But this has already been established for isoxazolines of formula (I) (see point 3.3.2). An improved treatment (such as with higher effectiveness or reduced amount of drug) which would be conditioned on an improved bioavailability is not claimed. The argument of the appellant is therefore not relevant when assessing sufficiency of disclosure of claim 16.

3.3.6 Finally, the lack of activity of the R-enantiomer of fluralaner (compound 11-1) against fleas observed under specific conditions in a single example (see D6, example 3 table 5) is not sufficient to question the sufficiency of disclosure.

3.3.7 As a result, the Board considers that the subject-matter of claim 16 is sufficiently disclosed.

3.4 Hence, the main request fulfills the requirements of Article 83 EPC.

4. Novelty

The appellant did not pursue in the appeal stage the objection under Article 100(a) EPC in combination with Article 54 EPC. In line with the impugned decision, the

Board considers that the main request fulfills the requirements of Article 54 EPC.

5. Inventive step

5.1 Closest prior art

5.1.1 The main request relates to a soft chew composition comprising an isoxazoline of formula (I) as defined in claim 1, a solid carrier and a specific solvent (namely 2-pyrrolidone, DMAC or mixtures thereof). The composition is useful in controlling parasite infestation in animals.

5.1.2 During oral proceedings, both parties considered D6 to represent the closest prior art. D6 discloses isoxazolines of formula (I) or structurally similar compounds as well as safe compositions containing them for parasite control in animals. Various dosage forms for oral administration are described (see paragraph [0232]). Example 6 group A reports the efficacy of an oral tablet containing fluralaner (compound 11-1) to control fleas and ticks after administration to dogs. In particular, mean plasma concentrations are reported in this example.

D8, mentioned as alternative starting point by the appellant in the written proceedings, also discloses anti-parasitic isooxazoline compounds as well as veterinary formulations comprising them and which may be administered *via* various routes including oral route. However D8 does not provide any information regarding the pharmacokinetics (PK) properties of such orally administered formulations. In particular, the testing in method C page 104 referred to by the appellant is merely an in vitro assay, which cannot

provide any indication regarding PK profile. Furthermore, the solvents mentioned on pages 54 to 55 relate to spot-on compositions and do not appear to have been disclosed in the context of chewable compositions.

5.1.3 As a consequence, the Board considers D6 to represent the most suitable starting point to the assessment of inventive step.

5.2 Distinguishing features

It was undisputed that the composition of claim 1 of the main request differs from the one of the closest embodiment of D6, namely example 6 group A, in that (i) it is a soft chewable composition, (ii) which contains a specific solvent, namely 2-pyrrolidone, DMAC or mixtures thereof.

5.3 Partial problem approach

5.3.1 Regarding the technical effects associated with these distinguishing features and their relationship, the appellant considered that:

- no particular effect had been demonstrated for the formulation as a soft chew besides the commonly known property of being convenient for oral administration (see paragraph [0007] of the patent),
- it had not been made credible that an increased bioavailability would also be obtained in absence of pre-dissolution of the drug in the solvent (see paragraphs [0032] to [0036] of the patent), *i.e.* the alleged effect had not been credibly substantiated over the entire claimed range.

The appellant further argued that the two distinguishing features were not interrelated, for the reasons described below.

- The original application related in general to a solid oral dosage form and was not limited to a soft chew composition. Moreover, the process of dissolution / adsorption was described in the published application as applicable to various oral dosage forms and was thus not limited to the preparation of a soft chew (see application as published, page 17 lines 9-15). D21 would further confirm that any dosage form may be prepared using this technique (see page 173, right column, last paragraph, first sentence).
- While the modification of the formulation from a tablet to a soft chew generally required to modify the excipients used, it did not necessarily require the addition of a solvent. Soft chews without solvent were indeed described in the patent (see control formulation of example 7 and formulations 13-009, 13-011 and 13-013 of example 8) as well as in D26. Any effect linked to the solvent was thus applicable to any solid dosage form.

The appellant therefore considered that the partial problem approach should be applied.

5.3.2 The Board considers that both features cannot be entirely separated because they are to some extent functionally related. All the excipients contained in a formulation will to a smaller or larger extent contribute to the final form thereof. The formulation as a chewable composition instead of as a tablet implies to modify the excipients, in particular it may, even if it does not necessarily have to, require the addition of solvents. Furthermore, the comparative

tests performed in the present case focus on the addition of the claimed solvents, but always in the context of a chewable composition. Any effect due to the addition of the claimed solvent has thus been shown for a chewable dosage form and may be conditioned thereupon. The chewable composition and the specific solvent cannot therefore be considered as a mere aggregation of features.

Hence, the Board considers that a partial problem approach is not appropriate in the present case.

5.4 Technical effect and objective technical problem

5.4.1 The respondent stated that an increased bioavailability would be obtained for the claimed chewable compositions, as substantiated in examples 7 to 8 of the patent and in D26 and D27.

5.4.2 However, none of these data substantiate that an increased bioavailability compared to the closest prior art can be credibly achieved for all the claimed soft chew compositions. The reasons are detailed below.

(a) A comparison of a chew according to the invention (Chew 2) and a tablet (Tablet 1) was performed in D26 and appears to indicate an improved Cmax for the chew according to the invention. However the tested tablet differs from the tablet of D6 (example 6 group A) in the relative amount of active ingredient as well as the nature and relative amounts of excipients. This data cannot therefore substantiate an improvement directly linked to the distinguishing feature over the closest prior art.

(b) Contrary to the opinion of the respondent, the results provided in examples 7 to 8 of the patent, in D26 and D27 do also not allow to conclude that the sole addition of the claimed solvents result in an improved bioavailability.

The chews of examples 7 and 8 of the patent as well as the chews of D26 differ indeed from each other not only in the addition of the claimed solvent but also in the nature and amount of several excipients. It follows that any observed effect cannot be attributed to the addition of the claimed solvent. In this context the respondent argued that, in D26, the composition according to the invention (Chew 2) had some of those features (amount of active agent, absence of corn starch, amounts of sodium starch, amounts of sodium lauryl sulfate, nature and amount of PEG) in common with the comparative Chew 1 and/or the comparative Chew 3, so that an effect of these features on the increase in bioavailability could be excluded. This argument is not convincing because Chew 2 of D26 still differs by more than one further feature from each of Chews 1 and 3.

The chews according to the invention used in D27 differ from the control chew only in the addition of the claimed solvents and accordingly reduced amounts of glycerol and soybean oil. However, the results of D27 were obtained under specific conditions, in particular with a specific preparation process, namely the pre-dissolution of the isoxazoline in the solvent prior to the adsorption on the solid carrier. This process is described in the patent itself as responsible for the increase of bioavailability (see paragraphs

[0033]-[0034] and [0071]-[0072]). According to these passages it is not merely the addition of solvent *per se* but also its process of addition that lead to the observed increased bioavailability. Hence, in view of the teaching of the patent, it cannot be considered that the effect obtained under these conditions will necessarily also occur upon mere mixing of all the components without prior dissolution of the isoxazoline. However this embodiment also forms part of the claims. The Board thus considers that an improved bioavailability due to the addition of the specific solvents in chew compositions has not been rendered credible over the whole scope of the claims.

In this respect, the respondent argued that the improved bioavailability observed in D27 would not be limited to the process used. When mixing all ingredients together, at least part of the drug would also get dissolved in the solvent, so that an improved bioavailability would also be achieved even if to a lesser extent. In the absence of any evidence thereof, this argument is not convincing. In particular, this argument remains vague as to the extent of dissolution of the drug and the actual significance thereof for the bioavailability.

5.4.3 Accordingly, the objective technical problem can only be formulated as the provision of an alternative oral dosage form comprising an isoxazoline of formula (I) for use in controlling parasitic infestation.

5.5 Obviousness

5.5.1 The Board considers that the idea of preparing a soft chew is at least broadly suggested in D6, which recites soft chews in a list of equally disclosed dosage forms (see paragraph [0232]). The question to be answered is thus whether the skilled person would have been prompted in view of the prior art to use the present specific solvent(s), namely DMAC and/or 2-pyrrolidone, to prepare a soft chew containing an isoxazoline of formula (I).

5.5.2 The appellant argued that the dissolution / adsorption technique was a well-known technique to increase the solubility and bioavailability of poorly water soluble drugs and referred to D13 (pages 1281 and 1283), D14 ("solvent deposition technique", page 16, page 17 table 1), D21 (solvent deposition technique, page 171, right column, lines 3-4; p 172, right column, point 2.6; p173, right column, last paragraph; page 174, left column, 2nd paragraph), D25 (page 247, general disclosure of solid dispersion) and D33 (see "Introduction" and the paragraph bridging pages 108 and 109). Since the present isoxazolines were commonly known as poorly water soluble drugs, the skilled person would have used this technique to formulate them. In this context the appellant mentioned that afoxolaner was a BSC Class II drug, which drugs were the subject of D33. Besides D33 disclosed a great variety of active agents including some used in veterinary treatments (see *e.g.* prednisolone or indomethacine in Table 2), which would provide a further hint to apply this technique to the present isoxazolines.

During oral proceedings the appellant concentrated on the combination of D6 and either D21 or D33. These two

documents disclosed the present solvents as suitable solvents for the dissolution / adsorption technique (D21, see *e.g.* page 172, right column, point 2.6 and Figure 4; D33, see *e.g.* page 110 under "non volatile solvent" and Table 2 page 114). According to the appellant, the skilled person would have furthermore known that 2-pyrrolidone and DMAC were compatible with an oral administration, as revealed by D16 and D15 (see D16, page 600, right column, item 7. and D15, page 241, left column, item 7).

Hence the appellant concluded that the skilled person would have arrived at the present soft chews without exercising inventive skills.

5.5.3 The Board observes that the cited prior art documents disclose neither the use of DMAC or 2-pyrrolidone in soft chews nor as solvent of fluralaner, *i.e.* the compound of the closest prior art formulation (see compound 11-1 in D6). The common poor water solubility of the compounds of D21 and D33 and the present isoxazolines is not considered to constitute a sufficient hint to the use of specifically DMAC or 2-pyrrolidone as solvent when preparing an alternative formulation of fluralaner. Neither the fact that one isoxazoline (afoxolaner) belongs to the BSC class II nor the applicability of some active agents disclosed in D33 in the veterinary field is sufficient to fill this gap. Moreover, the mere suitability of 2-pyrrolidone and DMAC for oral administration does not necessarily imply that they would be suitable for the preparation of soft chews. The appellant's reasoning requires hindsight.

The skilled person, if prompted to prepare a soft chew based on the general disclosure of D6, would have

consulted a document relating to the preparation of soft chews, such as D1 or D7 (the sole documents on file disclosing chewable formulations). These documents do not disclose 2-pyrrolidone or DMAC.

The Board considers therefore that the skilled person would have had no motivation to modify the formulation of example 6 group A of D6 by using DMAC or 2-pyrrolidone to prepare a soft chew.

5.6 Hence the claimed compositions as well as their preparation and the medical use thereof are inventive. Accordingly, the main request involves an inventive step (Article 56 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