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**Datasheet for the decision
of 29 March 2019**

Case Number: T 0887/14 - 3.3.02

Application Number: 01971479.9

Publication Number: 1435786

IPC: A01N45/02

Language of the proceedings: EN

Title of invention:
PESTICIDAL FORMULATIONS

Patent Proprietor:
Elanco US Inc.

Opponent:
DONNELLY, Martin

Headword:

Relevant legal provisions:
EPC Art. 123(2), 56, 83

Keyword:
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:

T 1317/13

Catchword:



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Case Number: T 0887/14 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 29 March 2019

Appellant: DONNELLY, Martin
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Decision under appeal: **Interlocutory decision of the Opposition
Division of the European Patent Office posted on
31 January 2014 concerning maintenance of the
European Patent No. 1435786 in amended form.**

Composition of the Board:

Chairman M. O. Müller
Members: P. O'Sullivan
P. de Heij

Summary of Facts and Submissions

- I. The opponent's appeal lies from the interlocutory decision of the opposition division according to which European patent EP 1 435 786 in amended form and the invention to which it relates were found to meet the requirements of the EPC.

- II. The patent was opposed under Article 100(a), (b) and (c) EPC on the grounds that the claims thereof lacked novelty and did not involve an inventive step, the invention disclosed therein was not disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, and its subject-matter extended beyond the content of the application as filed.

- III. According to the decision under appeal, the set of claims and adapted description according to the first auxiliary request, filed during oral proceedings, met the requirements of the EPC:
 - (a) Although not providing literal support, the subject-matter of claim 1 was directly and unambiguously derivable from the application as filed. The requirements of Article 123(2) EPC were thus met.

 - (b) Claim 1 of auxiliary request 1 also met the requirements of Article 123(3) EPC.

 - (c) The invention underlying the claims was considered sufficiently disclosed, and the subject-matter of claim 1 was novel over the disclosure in D9.

(d) In the assessment of inventive step, D4 was the closest prior art. A synergistic effect was recognised for the spinosad/ivermectin formulation of example 2 of the patent and for the spinosad/milbemycin oxime formulation of the post-published evidence D23. The objective technical problem was the provision of an improved method for the control of fleas on dogs and cats, and the solution provided by claim 1 involved an inventive step.

IV. The following evidence *inter alia* was cited during opposition proceedings:

- D4: WO 01/11963
- D8: Snyder *et al.* (2012), *Veterinary Parasitology*, 184, pp 284-290
- D12: Declaration of W. Hunter White dated 12 November 2007, and attachments
- D13: Declaration of W. Hunter White dated 14 August 2007, and attachments
- D14: Declaration of W. Hunter White dated 10 February 2009, and attachments
- D15: Declaration of D. E Snyder dated 12 November 2007, and attachments
- D16: Declaration by D. E Snyder and S. Wiseman dated 8 November 2012
- D19: R. Hollingworth, *Agrochemical Discovery*, Chapter 21, ACS Symposium Series, pp 238-255
- D23: Declaration of W. Hunter White, S. Wiseman and D. Snyder
- D26: "Evaluation of the Efficacy of Spinosad Administered Orally to Fed Versus Fasted Dogs for the Treatment and Control of Adult Cat Fleas (*Ctenocephalides felis*)", Study No. T9C370103
- D28: Banks *et al.*, *Bioorg. Med. Chem.* 2000, 8, pp 2017-2025

- D29: Zakson-Aiken *et al.*, *J. Med. Entomology*, 2001, 38(4)
- D30: Freedom of information summary for Comfortis®, 2007
- D38: *The Veterinary Formulary* (2001) 5th Edition, pp 219-236

V. Further evidence was filed during written appeal proceedings (denoted D41-D43 with the appellant's statement setting out the grounds of appeal; D44-D45 with the respondent's reply thereto; D46-D53 with the appellant's letter of 10 March 2014; and D54-D56 with the respondent's letter of 30 September 2015), among which the following was addressed during oral proceedings before the board:

- D56: Statistical analysis by Dr Scott Wiseman dated 29 September 2015

VI. The appellant (opponent) requested that the decision under appeal be set aside and the patent be revoked in its entirety.

VII. The respondent requested that the appeal be dismissed as main request, or as an auxiliary measure, that the patent be maintained on the basis of the set of claims according to auxiliary request 1 filed with the reply to the statement of grounds of appeal, or the set of claims of auxiliary request 2 filed with the letter of 30 September 2015.

The main request corresponded to the first auxiliary request found allowable by the opposition division, as confirmed during oral proceedings (see minutes of oral proceedings).

VIII. A communication of the board was sent in preparation for oral proceedings. Therein the board *inter alia* provided the preliminary opinion that the requirements of Article 123(2) EPC were fulfilled, and noted that the issue of sufficiency of disclosure was closely related to the discussion of whether there was sufficient evidence of synergy for the claimed formulation.

IX. Independent claim 1 of the main request reads as follows:

"A formulation for use in controlling or preventing fleas in dogs or cats, said formulation including an effective amount of a systemically active composition comprising a synergistic combination of spinosad, or salt thereof, and a macrocyclic lactone selected from: ivermectin, abamectin, moxidectin, doramectin, eprinomectin and milbemycin and an acceptable carrier, diluent or excipient, wherein said formulation is to be topically, orally or parenterally administered."

X. Oral proceedings were held before the board on 29 March 2019.

XI. The appellant's arguments, insofar as relevant to the present decision, may be summarised as follows:

Main request

Admittance of evidence - D56

D56 was not submitted with the reply to the grounds of appeal and was thus late filed. It was not more relevant than the evidence already on file and should not be admitted into the proceedings.

Amendments (Article 123(2) EPC)

The subject-matter of claim 1 resulted from selections from two or more lists and thus generated a new combination of features, resulting in an unwarranted advantage for the patentee in violation of G 1/93 and consequently Article 123(2) EPC. Specifically, "fleas" were chosen from the broad class of pests in claim 1, "dogs and cats" were chosen as the hosts, "topically, orally or parenterally" as the modes of administration, "spinosad" from the A83543 compounds, and the list in claim 1 from the general class of macrocyclic lactones.

Sufficiency of Disclosure

The experimental data relied on by the respondent did not plausibly demonstrate synergy across the scope of the claims and D8 provided proof that synergy was not obtained. Furthermore, the extrapolation of synergy to the whole group of macrocyclic lactones recited in claim 1 was not justified.

Inventive step

D4, in particular the disclosure on page 8 (lines 7 - 13) was the closest prior art. Even if the text on page 3, line 23 - page 4, line 2 was to be considered as the most appropriate starting point, as was argued by the respondent, the skilled person would not have excluded the text on page 8. The distinguishing features of claim 1 over D4 were the selection of spinosad from the group of spinosyns, and the selection of avermectins and milbemycins from the group listed in D4 (page 8). The technical effect, in view of the conclusion reached by the board during oral proceedings with respect to

sufficiency of disclosure, was the provision of a synergistic combination. The technical problem was the provision of an improved treatment of fleas in dogs or cats. The solution provided by claim 1 did not involve an inventive step:

- in view of D4 in combination with D2. D2 related to synergistic combinations of emamectin with further pesticidally active compounds, among which spinosad was listed. Although emamectin was not listed in claim 1, it belonged to the same class of macrocyclic lactones and, by the same rationale as that used to extrapolate the synergistic effect (in the patent) from ivermectin to the other macrolactones recited in claim 1, the skilled person would extrapolate an effect from emamectin to the same said macrolactones. D2 also related to the treatment of domestic and farm animals (page 13, penultimate paragraph), and fleas (Siphonaptera) were among the pests mentioned in referenced document D43, cited in D2 (page 12, final paragraph). In the examples, a synergistic effect was said to be shown. Thus the skilled person would learn from D2 that a combination of a macrolactone recited in claim 1 with spinosad would provide a synergistic effect, and would thereby arrive at the subject-matter of claim 1. Furthermore, D19, which disclosed the mechanism of action of spinosad (page 242) would provide additional motivation for the skilled person to combine D4 with D2.

- Furthermore, the discovery of synergism was a mere bonus effect in view of the teaching of D4

and thus had to be disregarded for the purpose of assessing inventive step.

XII. The respondent's arguments, insofar as relevant to the present decision may be summarised as follows:

Main request

Admittance of evidence - D56

D56 was filed in response to statistical arguments submitted for the first time with the appellant's counter-response dated 10 March 2015 and accordingly should be admitted into the proceedings.

Amendments (Article 123(2) EPC)

The subject-matter of claim 1 was directly and unambiguously derivable from the application as filed. The question raised by the appellant as to whether the limitation in the claims provide an unwarranted advantage to the patentee was not relevant.

Sufficiency of Disclosure

The application as filed, example 2, and the subsequent post-filed studies D12, D13, D14, D15 and D26 rendered plausible the existence of synergy both *in vitro* and *in vivo*. The appellant's criticism of these tests failed to demonstrate the contrary. Furthermore, contrary to the appellant's argument, D8 even proved that synergy was present. Lastly, extrapolation of the effect to other macrocyclic lactones of the same class was plausible.

Inventive step

D4 was the closest prior art. The skilled person would start from the passage in D4 disclosing cats and dogs, viz. on page 3. The further passage on page 8 merely taught the inclusion of one or more other compounds "*that have activity against the specific ectoparasite or endoparasite to be controlled..*". Since ivermectin and milbemycins were known from D28 and D29 to have no activity against fleas, the skilled person would never consider combining them with spinosad with a view to providing an improved treatment for fleas in dogs or cats. The focus of D2 was the treatment of pests on plants, it was extremely general and the alleged synergy with emamectin displayed by the listed compounds was speculative. The argument that the skilled person would additionally look to the mechanism of action to investigate what could potentially be combined to provide synergy must fail since such investigation would constitute a research program beyond the ability of the skilled person. Additionally, the presence of synergy was not a mere "bonus effect", since D4 did not teach the skilled person to arrive at subject-matter falling with the scope of claim 1 even when disregarding the effect of synergy. Consequently, claim 1 involved an inventive step.

Reasons for the Decision

Main request

1. Amendments, Article 123(2) EPC
 - 1.1 The appellant submitted that the subject-matter of claim 1 resulted from selections from two or more lists and thus generated a new combination of features, resulting in an unwarranted advantage for the patentee in violation of G 1/93.
 - 1.2 Specifically it was argued that starting from claim 18 as filed, that the following choices were necessary in order to arrive at the subject-matter of claim 1:
 - (a) "fleas" from the broad class of pests (Phthiraptera, Siphonaptera and Acarina) in original claim 18
 - (b) "dogs and cats" as the domestic animals as indirectly referred to in original claim 18 (by way of referring back to original claim 8)
 - (c) "topically, orally or parenterally" as the modes of administration
 - (d) "spinosad" from the A83543 compounds referred to in original claim 1 and
 - (e) ivermectin, abamectin, moxidectin, doramectin, eprinomectin and milbemycin from the general class of macrocyclic lactones cited on page 17, lines 5-9.
 - 1.3 In order for the requirements of Article 123(2) EPC to be fulfilled, the only relevant test is that the claimed subject-matter must be (at least implicitly) directly and unambiguously derivable from the application as filed (the so-called "gold standard").

If that is the case, there can be no "unwarranted advantage" in the sense of G 1/93.

1.4 Claim 18 of the application as filed depends on claim 8 which in turn depends on claim 1. This combination of claims discloses a formulation for use in controlling or preventing pests (among which, Siphonaptera, i.e. fleas, is mentioned) including an acceptable carrier, diluent or excipient, and comprising a synergistic combination of at least one A83543 compound and at least one macrocyclic lactone. "A83543 compounds" refer to a family of related compounds known as spinosyns (application, page 3, lines 32-33).

1.5 Among the spinosyns, it is clear from the application as filed that "spinosad" is the spinosyn compound of choice (page 11, line 31-33; page 17, lines 5-9 and the examples all of which employ spinosad). The "salt thereof" in claim 1 at issue find basis on page 20, lines 18-26, disclosing that in the formulations of the invention the spinosyn compound may be present as a salt. The macrocyclic lactones of claim 1 at issue to be combined with spinosad are listed on page 17, lines 5-9, i.e. in the very same paragraph in which spinosad is mentioned as a specific spinosyn compound. There is thus a clear pointer present in the application as filed to use a composition as defined in claim 1 (above selections (d) and (e)). In fact, no choice is needed at all for the macrocyclic lactones since those defined in claim 1 represent the broadest embodiment disclosed in the description of the application as filed.

1.6 Subsequently, on the same page of the application as filed, namely in the paragraph bridging pages 17 and 18, it is stated that topically, orally or parenterally administered formulations of the invention act to

control various different pests on hosts; a list of hosts is provided. The final sentence of this paragraph reads "[a]lso more typically, a topically, orally or parenterally administered formulation of the present invention acts to control lice and ticks in cattle, and **fleas in both cats and dogs**" (emphasis added).

1.7 Thus the specific modes of administration, the pest and the animals to be treated are disclosed in combination as being applicable to a 'formulation of the present invention' in general. No multiple selection ((a) to (c) above) is required in this respect.

1.8 Hence, claim 1 does not result from an unallowable selection from a number of lists.

1.9 It follows that the requirements of Article 123(2) EPC are fulfilled.

2. Admittance of evidence - D56

2.1 D56 was filed by the respondent with the letter of 30 September 2015. According to D56 itself (second paragraph), its purpose was to counter the assertion of the appellant made in the submission of March 2015, that the variation in efficacy when comparing the results presented in D15 with those of D26 was within experimental variance.

This argument is presented in the letter of the appellant of 10 March 2015 (in particular paragraphs 31-35). D56 is drafted by a statistician and sets out to demonstrate that in contrast to the submissions of the appellant, the observed differences (D15 versus D26) are attributable to the synergy between spinosad and milbemycin oxime. D56 consequently represents a

reasonable and timely reaction to said submissions. The board therefore admitted D56 into the proceedings in accordance with Article 13(1) RPBA.

3. Sufficiency of disclosure

3.1 Claim 1 is a purpose-limited product claim. It recites that the formulation thereof includes "*an effective amount of a systemically active composition comprising a synergistic combination of spinosad ... and a macrocyclic lactone selected from ...*". Thus the attainment of a **synergistic** effect from the combination recited, in controlling or preventing fleas in cats or dogs, is a functional technical feature of the claim.

3.2 It was undisputed by the parties that in order for the invention to be considered disclosed in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art, he must be capable of obtaining, without undue burden, the claimed **synergistic** effect in a dog or cat.

3.3 Thus it must be determined whether synergism has been plausibly demonstrated across the breadth of the claim, based on the evidence on file.

3.4 The respondent submitted that evidence of said synergy is provided by:

- example 2 of the patent
- tests reports D12, D13 and D14, and
- test report D15 when compared with D26

3.4.1 Example 2 of the patent is an *in vitro* assay to investigate synergism between spinosad and ivermectin in fleas using an artificial membrane system for adult

fleas ("the artificial dog"). In the test, groups of fleas fed on blood containing a range of concentrations (expressed as a percentage of the calculated LC₉₀ value) of spinosad or ivermectin and mortality is assessed after 24 hours. The fleas were also exposed to combinations of various ratios of each chemical, viz. 1:1, 1:4, 4:1, 9:1 and 1:9. Significant potentiation (i.e. synergy) was found for most of the combinations tested, that with a spinosad:ivermectin ratio of 4:1 and 9:1 being most pronounced. Thus synergy for the combination of spinosad with ivermectin has been demonstrated *in vitro*.

3.4.2 D12, D13 and D14 all concern *in vitro* experiments on the adult stable fly to test for synergy between spinosad and milbemycin oxime. The tests of D12 conclude that the 1:4, 1:9, 1:19, 4:1 and 9:1 ratios of spinosad:milbemycin reflect progressively increasing degrees of synergy, with the 19:1 ratio of spinosad to milbemycin exhibiting the greatest synergy. (D12, "conclusions"; table 1). In D13 it was reconfirmed that synergy was observed at the 19:1 ratio of spinosad:milbemycin, and extended to include the corresponding 99:1 ratio (D13, table 1 and "conclusion"). Finally, D14 again confirms synergy for the 19:1 ratio, and demonstrates that synergy is also observed for the ratios 1:2 and 2:1 (D14, "conclusion", and table 1). Consequently, synergy for the combination of spinosad with milbemycin oxime has been demonstrated *in vitro* for the stable fly.

3.4.3 D15 is an *in vivo* laboratory study to test the efficacy of a combination of spinosad with milbemycin oxime administered orally to dogs for the treatment of adult cat fleas. D15 does not provide comparative results for spinosad alone. D26 on the other hand concerns the

evaluation of the *in vivo* efficacy of spinosad administered orally to dogs for the treatment of adult cat fleas. A comparison between the results provided in D15 with those of D26 was provided in declaration D23 (sections 12-14). In particular, the raw data provided in table 2 of D23 shows an obvious improvement in D15 in the reduction of live fleas recovered from treated dogs on day 30 after the treatment, compared to the reduction recorded in D26. Thus, on first view, a comparison of the data in D15 with that in D26 demonstrates synergy for the combinations *in vivo*, in a dog.

3.5 The appellant argued that none of the above conclusions can serve as evidence of synergy, since

- example 2 of the patent was fundamentally flawed and not suitable for demonstrating synergy because it was an *in vitro* study, not reflecting the actual claimed use *in vivo*, in dogs and cats. Secondly, the doses of ivermectin used in example 2 would be unacceptably toxic for dogs, as demonstrated by on the one hand the dose of ivermectin required in dogs for LC₉₀ at 24 hours (47.5 mg/kg; D29) and the minimum dose of 6 mg/kg in example 2 (1/8 of the LC₉₀), and on the other hand the maximum recommended dose of ivermectin in dogs (600 µm/kg daily; D38). Furthermore, a large number of dog breeds were intolerant to ivermectin,
- The stable fly model employed in D12-D14 could not be relied upon to demonstrate synergy between spinosad and milbemycin due to the relative sensitivities of fleas and flies to the two active compounds being very different; and

- the *in vivo* studies in particular in D8 in which spinosad was directly compared with combinations of spinosad and milbemyacin were more reliable than the data extracted from D15 and D26, the latter representing two separate studies at two separate study centres, thereby involving a significant number of variables which would impact on the results to the extent that the alleged improvement could not be attributed to an improvement caused by synergy. In particular, the differing C_{max} values (the peak serum concentration that the active agent achieves) for spinosad in the combination according to D15 (3000 ng/ml; paragraph below table 1) compared to that for the D26 study for spinosad alone (2502 ng/ml; inferred from D26 and D30) was enough to account for the difference in the results, presented in D23 (in particular tables 1 - 3). Thus, it was not a surprise that the combination of D15 was more effective, since the blood of the dogs contained a higher maximum concentration of spinosad. In contrast, the D8 study, in particular the data for day 37 (D8, table 1), showed a geometric mean efficacy for the combination versus spinosad alone of 98.77% and 97.69% respectively. The difference between the two values was statistically insignificant, thus demonstrating that the combination of spinosad with milbemyacin oxime *in vivo* did not display synergy.

- the extrapolation of synergy from ivermectin to milbemyacin and the group of macrolactones recited in claim 1 was not justified, in particular since the patent did not provide *in vivo* data which would serve as evidence that synergy could reasonably be expected over the entire group.

- 3.6 Each of these aspects shall be addressed by the board in the following:
- 3.6.1 As noted above, example 2 of the patent demonstrates a synergy for the combination of spinosad with ivermectin *in vitro*. This test, although *in vitro* in the sense that it involved an "artificial" rather than a living dog, is nevertheless *in vivo* as far as the fleas are concerned, and thus cannot be characterised as fully *in vitro*. The test shows that for live fleas, exposure to the combination in blood is synergistic for most ratios tested.
- 3.6.2 While it may be the case that certain doses of ivermectin used in example 2 are toxic to dogs as submitted by the appellant, this does not take away from the synergism demonstrated therein, and the fact, as noted by the respondent, that the example did not set out to investigate suitable doses for application to a dog. Furthermore, it has not been demonstrated that non-toxic doses of ivermectin in combination with spinosad would **not** exhibit synergism. If it were to be accepted that the toxicity of ivermectin to dogs was part of the common general knowledge of the skilled person, then for the purpose of sufficiency of disclosure, it must also be accepted that the skilled person would know to avoid dosage formulations comprising a toxic dose.
- 3.6.3 The *in vitro* tests of D12-D14 were performed with synergism being assessed using the activity of the combination concerned against the stable fly. As submitted by the respondent, the stable fly has been used by Elanco as a model for fleas for many years. This at least indicates that it has a certain level of validity. Furthermore, according to the declaration D23

(paragraph 1), the stable fly bioassay is repeatable and can be used to assess the intrinsic systemic insecticidal activity of various compounds against voracious blood sucking pests, to which group both fleas and stable flies belong. Lastly, the stable fly assay had previously been found reliable as a predictive model for activity against fleas: in tests involving both stable flies and fleas, the rank order of the magnitude of activity was found to be the same for fleas and stable flies (D23, paragraph 2).

3.6.4 In contrast hereto, the appellant submits that based on vastly different EC₉₀ values for spinosad in a stable fly and a flea, it is impossible to extrapolate a finding of synergy in a stable fly to a fleas because they do not have parallel sensitivities to *both* ingredients. However, this is nothing more than speculation, unsupported by any plausible evidence. In particular, even if a significant difference in EC₉₀ values were to be accepted, there is no evidence that this would render the stable fly model unsuitable for extrapolation of the results to potential synergy in fleas. Consequently, the arguments of the appellant are insufficient to shift the burden of proof to the respondent with regard to the plausibility of the results provided in D12-D14.

3.6.5 A similar situation exists with respect to the *in vivo* synergy attributed by the respondent to the comparison of the results of tests of D15 with those of D26. The question to be answered is whether a synergistic effect has been rendered plausible by said comparison, and if so, whether D8 demonstrates the contrary and holds sufficient evidentiary value to cast doubt thereon.

- 3.6.6 The appellant's allegation that the differences between the data in D15 and D26 are due to the fact that the data were generated in different study centers is nothing but an unsubstantiated allegation. No evidence has been filed rendering this statement plausible.
- 3.6.7 The appellant focuses on differing C_{\max} values in the respective studies as being a potential source of the improvement (supra). However, as noted by the respondent, there is no evidence that the C_{\max} value would be conclusive in determining the end result.
- 3.6.8 On the other hand, without needing to determine whether the geometric mean or the arithmetic mean are more valid, the underlying data in D23 (table 2) speaks for itself. Thus, for example, 44 days after applying the combination treatment of D15, 45 live fleas were recovered, compared to 96 after day 30 in the treatment of D26 using spinosad alone. Thus, without evidence to the contrary, the data presented in particular in D23, table 2, plausibly supports the presence of synergy.
- 3.6.9 With regard to whether D8 is sufficient to cast doubt on this data, the following applies. As noted by the respondent, and detailed in declaration D16, D8, which the appellant submits as proof of lack of synergy, was set up to evaluate and confirm the non-interference of spinosad and milbemycin oxime (with each other) for the treatment in dogs of flea infestations and adult hookworm infections (D8, abstract; in written proceedings the appellant focused on D36 with regard this argument, choosing to argue starting from D8 only during oral proceedings). The board agrees with the respondent that one must be cautious in drawing specific conclusions regarding the presence or absence of synergy from a study not designed for that purpose.

Thus the results in D8 which demonstrate that spinosad and milbemycin do not negatively influence each other in the treatment of different pests are not necessarily appropriate for demonstrating that under suitable test conditions, spinosad and milbemycin will not act synergistically in the treatment of fleas on dogs.

3.6.10 Furthermore, the appellant's argument that the data in D8 for day 37 (table 1) proves that there is no synergism is at least questionable. At least on first view, the data appears to indeed show an improvement for the combination (98.77% versus 97.69% efficacy). The appellant contends that a statistician would have recognised that instead of the 8 dogs in D8, 51 dogs per treatment group would have had to be tested to have 80% power to declare a statistically significant synergy. However, in view of the fact that all that can be deduced from the data as such is a synergistic improvement, and in the absence of any evidence from the appellant that with a sufficiently high number of dogs, this improvement would not have been present, D8 cannot cast doubt on the synergy between spinosad and milbemycin found by comparing the results of D15 and D26.

3.6.11 With regard to whether it is plausible that other macrocyclic lactones of the same class recited in claim 1 would also share synergy with spinosad, the board notes that the patent itself provides a plausible mechanistic explanation of why this would be the case (paragraph [0051]). In the absence of any evidence to the contrary, the board sees no reason not to accept this as a reasonable assumption. The board also sees no reason to reject said explanation due to the lack of *in vivo* data in the patent, as argued by the appellant, since as mentioned above, the *in vitro* test according

to example 2 thereof may be considered *in vivo* at least as far as the fleas are concerned.

3.6.12 In view of the above, the tests of example 2 of the patent, D12, D13, D14, D15 and D26 plausibly demonstrate that synergy is present in the majority of ratios tested, the only concrete exception being the 1:1 ratio described in D12 (see "Conclusions") which is said to "reflect a purely additive interaction" (between spinosad and milbemycin).

3.6.13 Consequently the board is in no doubt that it would be within the routine ability of the skilled person to arrive at appropriate synergistic ratios of spinosad to the specific macrolactone recited in claim 1 without undue burden.

3.7 It follows that the invention as defined according to the main request is sufficiently disclosed.

4. Inventive step (Article 56 EPC)

4.1 Closest prior art

4.1.1 The parties agreed that D4 represents a suitable closest prior art disclosure. The board sees no reason to differ, since D4 shares the same aim and objectives as those mentioned in the contested patent, i.e. the use of spinosyn (and specifically, spinosad) in controlling or preventing fleas in dogs or cats (D4, page 3, line 20 - page 4, line 2).

4.2 Problem solved

4.2.1 D4 discloses a method for controlling cat or dog fleas on a companion animal for a prolonged time comprising

orally administering a single dose of an effective amount of a spinosyn to the animal (page 3, line 23 - page 4, line 2). It also discloses that spinosyn can be combined with one or more other compounds that "*have activity against the specific ectoparasite or endoparasite to be controlled*"; avermectins and milbemycins are provided among the list of possible compounds (page 8, lines 7 - 13). Although there was some dispute among the parties as to which of these passages of D4 represents the more appropriate starting point for the skilled person, the board does not see this choice as being crucial to the outcome of this discussion, since the skilled person will assess the teaching of D4 as a whole, and thereby will take both disclosures into account independently of which he may consult first.

4.2.2 Claim 1 at issue differs from the disclosure in D4 in

- the selection of spinosad from the group of spinosyns and
- the selection of avermectins and milbemycins from the list in D4, page 8 (lines 10-13).

4.2.3 The effect of these differences, established in the discussion of sufficiency of disclosure, above, is synergism in the treatment of fleas on dogs or cats.

4.2.4 The objective technical problem may consequently be seen as the provision of an improved formulation for treating fleas in dogs or cats.

4.3 Obviousness

4.3.1 The appellant relied firstly on a combination of D4 with D2 and optionally, D19.

- 4.3.2 The board acknowledges that spinosad, a commercially available product and comprising mainly spinosyn A and spinosyn D (D4, page 5, lines 1 - 4) is mentioned throughout the description and used in all examples of D4. Consequently, it is the spinosyn of choice in D4.
- 4.3.3 It is also true that D4 suggests that the formulation of the invention may further include, in combination with the spinosyn component, one or more other compounds that *"have activity against the specific ectoparasite or endoparasite to be controlled"*. It is however undisputed by the appellant that avermectins and milbemycins were known not to be active against fleas (D28, introduction; D29, page 578, right hand column, "Discussion", first paragraph). It follows therefore that D4 does **not** teach the skilled person to combine spinosyns with avermectins or milbemycins for the treatment of fleas in dogs or cats.
- 4.3.4 According to the appellant, the skilled person would nevertheless have combined the teaching of D4 with that of D2 to arrive at the solution proposed in claim 1 at issue.
- 4.3.5 The board disagrees. In order to arrive at the subject-matter of claim 1 at issue starting at the disclosure in D4 and in view of the teaching of D2, the skilled person would be required to:
- realise that D2 was relevant to the technical problem posed, despite its focus on treating pests in plants rather than dogs or cats, and in particular pests of the order *Acarina* (D2, page 1, first two paragraphs);

- recognise, through reference in D2 to D43 (D2, page 12, final paragraph) that the compositions listed therein could be applied in the treatment of fleas, listed as one of a very long list of animal pests in D43 (page 6, line 46, "Siphonaptera"),
- apply this composition to treat fleas in dogs and cats (chosen from "domestic and farm animals" in the "[f]urther fields of application of the active ingredient mixtures" (D2, page 13, penultimate paragraph);
- accept as credible that all 185 listed compounds in D2, including spinosad, display synergy with emamectin in the treatment of all pests mentioned and referenced in D43, including fleas, and
- replace emamectin with any of the macrocyclic lactones recited in claim 1 at issue and belonging to the same class.

4.3.6 In view of the number of steps required, the implementation of this combination of steps would be beyond the routine ability of the skilled person. In particular, in view of the unambiguous knowledge in the art that avermectins and milbemycins were known not to be active against fleas (D28 and D29, supra), the skilled person, given the disclosure provided in D2, would not have considered that the authors thereof had discovered, against all expectation, that emamectin (which belongs to the avermectin family of macrocyclic lactones) displayed synergy with spinosad in the treatment of fleas in dogs and cats.

4.3.7 The skilled person would be much more likely to view the extremely broad teaching of D2 according to which

all 185 "compounds" mentioned were found to be "synergistic" as speculative and lacking in credibility. Firstly, although the list itself is already extensive, not all members thereof are "compounds", but rather are broadly generalised groups (see in particular entries (52) - (56), e.g. "an insect-active extract from a plant") for which successful synergy appears even less credible. Secondly, since it is not stated against which specific pests synergism is observed, it is simply not credible that synergism would apply to all possible combinations of active agents, for all listed and referenced pests, including fleas disclosed in the cross-referenced document D43.

- 4.3.8 With regard to the appellant's submission that D19, which discloses the mechanism of action of spinosad (page 242) would provide additional motivation for the skilled person to combine D4 with D2, the board concludes that such a step, in particular in view of the knowledge in the art that avermectins and milbemycins were inactive against fleas (supra), would constitute elements of a research programme, far beyond the routine abilities of the skilled person.
- 4.3.9 Consequently, the skilled person would not arrive in an obvious manner at the solution proposed by claim 1 at issue in view of D4 as closest prior art in combination with D2.
- 4.3.10 The appellant secondly argued that synergy in the treatment of fleas was to be regarded as a mere bonus effect which would inevitably result from carrying out the teaching of D4.

4.3.11 The appellant submits in particular that the combination as claimed would have been made from the teaching of D4 alone in order to provide a "broad spectrum" pesticide, e.g. for treating both fleas **and** another pest (such as the treatment of flea eggs and heartworm by "Sentinel", which comprises milbemycin oxime, see D41), citing in particular D4, page 6, lines 22-24, which states:

"Using oral formulations of spinosyns to systemically control ectoparasites of companion animals, as a single treatment modality or in combination with other commonly used ectoparasitocidal compounds, has several advantages"

and page 8, lines 7-8 which teaches the combination with one or more compounds *"that have activity against the specific ectoparasite or endoparasite to be controlled"*.

4.3.12 As confirmed in T 1317/13 cited by the appellant in support of his argument, in relation to unexpected effects in the context of the assessment of inventive step, it must already have been obvious for the skilled person to arrive at something falling within the terms of a claim, because an advantageous effect could be expected to result from the combination, in order for an extra (possibly unforeseen) effect to lack inventive step (T 1317/13, reasons, 21).

4.3.13 Therefore, in the present case, in order for the effect of synergy in the treatment of fleas to be considered merely as a "bonus effect", it would need to be obvious from the teaching of D4 to combine spinosad with avermectins or milbemycins to achieve the effect

referred to by the appellant, namely to provide a pesticide having a broad spectrum of activity.

4.3.14 However, there is nothing in D4 teaching a combination as claimed in order to achieve such a broad spectrum of activity. The passage cited above from D4, page 6 refers to ectoparasites exclusively, and thus does not refer to combinations including active agents for treating endoparasites such as heartworm. Similarly, the passage on page 8 refers to the specific parasite to be controlled, whether it be an ecto- or an endoparasite, and gives no indication that different agents for treating different parasites are intended to be combined. D4 consequently does not teach the combination of spinosad with avermectins or milbemycins to produce a broad spectrum effect in a single dose to be administered.

4.3.15 Since D4 does not teach the skilled person to combine the active agents disclosed therein, thereby leading him to a formulation falling within the terms of claim 1 at issue, it follows that the question of whether synergy in the treatment of fleas is to be considered as a bonus effect does not arise.

4.3.16 Consequently, the subject-matter of claim 1 involves an inventive step starting from D4.

4.3.17 In written appeal proceedings the appellant also suggested that D9 may serve as the closest prior art. As noted by the board in the communication sent in preparation of oral proceedings, D9 at least does not specifically relate to controlling or preventing fleas in cats or dogs, and is thus in terms of the number of features in common, further than D4 from the subject-matter of claim 1. It follows therefore that the

conclusions drawn above with respect to the choice of D4 as closest prior art apply *a fortiori* to the disclosure in D9.

- 4.4 It follows from the foregoing that the subject-matter of claim 1 and claim 2-6 dependent thereon involves an inventive step.
5. The set of claims according to the main request meets the requirements of the EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:



N. Maslin

M. O. Müller

Decision electronically authenticated