

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No. PCT/EP2018/080230	International filing date (day/month/year) 06.11.2018	Priority date (day/month/year) 07.11.2017
--	--	--

International Patent Classification (IPC) or both national classification and IPC
INV. C07D261/04 A61P33/14 A01N43/80 A61K31/42

Applicant
INTERVET INTERNATIONAL B.V.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Fax: +49 89 2399 - 4465	Date of completion of this opinion see form PCT/ISA/210	Authorized Officer Kiernan, Andrea Telephone No. +49 89 2399-0	
--	--	--	---

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43bis.1(a))
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13ter.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13ter.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13ter.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	<u>1-14, 18, 20-24</u>
	No: Claims	<u>15-17, 19</u>
Inventive step (IS)	Yes: Claims	<u>1-14, 20-24</u>
	No: Claims	<u>15-19</u>
Industrial applicability (IA)	Yes: Claims	<u>1-24</u>
	No: Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- | | |
|----|--|
| D1 | US 2014/121194 A1 |
| D2 | WO 2010/149727 A2 |
| D3 | WO 2011/149749 A1 |
| D4 | EP 2 308 857 A1 |
| D5 | XP021179157 (Kilp, S. et al., Parasites & Vectors, vol. 7, no. 1 (2014), p. 85-89) |

The application relates to a process for preparing large size isoxazoline particles which comprises initiating crystallization and then maintaining the temperature of the crystallization in the metastable region by removing, reheating and recycling a portion of the solvent thereby allowing the existing crystals to grow larger while minimizing the formation of newer smaller crystals. The desired result are particles having a volume weighted particle size distribution (d50) of between 75 and 120 μm and an average particle thickness of greater than 10 μm as measured by scanning electron microscopy (SEM).

Also claimed is an isoxazoline compound particle composition comprising particles with a thickness of greater than 10 μm as measured by scanning electron microscopy (SEM).

Novelty

The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of claims 15-17 and 19 is not new.

D1 discloses on page 11, paragraph [0096] particles of an isoxazoline compound having a diameter of 23 μm .

Present claim 16 is directed to an isoxaline compound particle composition comprising particles with a thickness of greater than 10 μm as measured by SEM. The expression "thickness" is not considered meaningful in the absence of other size limitations and thus not suitable to impart novelty over the disclosure of particles having a diameter in the claimed μm range.

Claims 17 and 19 merely contain a statement of a result to be achieved, without specifying the technical features necessary to achieve said result. Consequently, the subject-matter of these claims cannot impart novelty on claim 16.

Claim 15 is formulated as a product-by-process claim and relates to isoxazoline compound particles "produced by the process of any of claims 1-14".

The process steps do not impart novelty or an inventive step on the product thus produced. The process claims further delimit the isoxazoline particles in that they must comprise a compound of Formula I as defined in claims 1 and 2.

However, the isoxazoline derivatives disclosed in D1 also fall within the scope of present Formula I.

In the last paragraphs of process claims 1 and 2, it is stated that the desired particle dimensions are particles having a volume weighted particle size distribution (d50) of between 75 and 120 μm and an average particle thickness of greater than 10 μm as measured by scanning electron microscopy (SEM). However, such a stated desired outcome has no limiting effect on the product thus produced.

D1 is therefore considered novelty-destroying for claims 15-17 and 19.

Claims 1-14 and 20-24 relate to a process for the preparation of large size particles of isoxazoline derivatives of the general Formula I.

D3 (see page 12, Preparation Example 3) and D4 (see page 11, paragraph [0077]) also disclose methods for crystallizing isoxazoline derivatives falling within the scope of present Formula I (D3: afoxolaner, see page 4; D4: fluralaner, see page 4).

However, the removing, heating and returning a portion of the solvent as specified in present independent claims 1 and 2 or the resulting particle dimensions as specified in the last paragraph of claims 1 and 2 is not described.

Claims 1-14 and 20-24 thus appear to meet the requirements of Article 33(2) PCT.

Inventive Step

The present application does not meet the requirements of Article 33(3) PCT, because the subject-matter of claims 15-19 does not involve an inventive step.

As already discussed under Novelty above, the subject-matter of claims 15-17 and 19 is not novel. Moreover, it is observed that these claims are not restricted to particles of isoxazoline compounds of Formula I as defined in claims 1 and 2, but to particles of any isoxazoline derivative.

It is not apparent which technical problem is solved by the provision of particles of a certain size in the absence of any described common activity or use, and no inventive step can be acknowledged for this reason alone.

D4 discloses the isoxazoline derivative fluralaner (see page 4) and various methods for its crystallization (see page 11, paragraph [0077]).

The scope of claim 18 is not considered clear (see under Re Item VIII below).

The subject-matter of claim 18 could also be considered to differ from the teaching of D4 in that the particle size is not explicitly disclosed in D4.

However, present claim 18 in combination with claim 16 to which it refers does not specify an average particle size, but merely requires that the particle composition comprises particles with a thickness of greater than 10 μm . It thus appears unavoidable when using the methods described in D4 that a particle composition comprising at least some particles having said size is obtained.

As already mentioned under Novelty above, the feature "thickness" alone does not distinguish the claimed particles from particles having the same size or diameter.

Moreover, it is not apparent which technical problem is solved by the provision of fluralaner having the claimed particle size; the application does not contain any evidence of an effect or advantage in connection with the particle dimensions.

Consequently, the subject-matter of claim 18 is not considered inventive over the known fluralaner particles described in D4.

The same considerations apply to the isoxazoline compound particles disclosed in present claim 15 (Article 33(3) PCT).

The subject-matter of process claims 1-14 and 20-24 is not rendered obvious by the teaching of D3 and D4; these claims therefore meet the requirement of Article 33(3) PCT.

Industrial Applicability

Industrial applicability is acknowledged.

Re Item VII

Certain defects in the international application

According to Rule 6.4(c) PCT, all dependent claims should be grouped together to the extent and in the most practical way possible. Accordingly, dependent process claims 20-24 should be grouped together with process claims 1-14.

Re Item VIII

Certain observations on the international application

- 1 The expressions "about", "approximately" and "around" used in claims 1, 2, 5, 6, 10 and 21 as well as the corresponding passages in the description are vague and indefinite and render the scope of the claims unclear (Article 6 PCT).
- 2 Claims 1, 2, 5, 6, 9, 10, 11, 13, 16, 21 and 23 contain further preferred features which define a second scope of protection within one claim. This renders the scope of the claims unclear (Article 6 PCT).

It could also be argued that these features are simply non-limiting for these claims. In this case, they are superfluous, and the requirement of conciseness is not met (Article 6 PCT).

Such further preferred features have to be deleted or formulated as separate dependent claims.

- 3 Claim 15 discloses isoxazoline compound particles "produced by the process of any of claims 1-14", i.e. is formulated as a product-by-process claim. However, the scope of this claim is not clear in that it leaves the reader in doubt as to whether a product prepared by the claimed process, but which does not achieve the desired particle dimensions indicated at the end of claims 1 and 2 would also fall within the scope of claim 15.

Moreover, it is not certain that the particle dimensions stay the same when drying them as disclosed in process claim 14 to which claim 15 also refers (Article 6 PCT).

- 4 In claims 17 and 19, the subject-matter is defined in terms of a result to be achieved, without indicating the technical features necessary to achieve said result. These claims therefore do not meet the requirements of Article 5 and 6 PCT.

- 5 On page 7, line 24, "um" should probably read "µm (Article 6 PCT).

- 6 On page 7, lines 17-18, "(3A), (3B)" should probably read "(4A), (4B)" (Article 6 PCT).