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Case Number: T 1374/11 - 3.3.01

Application Number: 02796784.3

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Language of the proceedings: EN

Title of invention:
DRINKABLE PREPARATION COMPRISING KETOPROFEN AND USE THEREOF IN THE SIMULTANEOUS TREATMENT OF A GROUP OF ANIMALS OF RESPIRATORY DISEASES

Patent Proprietor:
LABORATORIOS DEL DR. ESTEVE, S.A.

Opponent:
Labiana Life Sciences, S.A.U.

Headword:
Treatment with drinkable ketoprofen/ESTEVE

Relevant legal provisions:
EPC Art. 56, 84, 123(2)
RPBA Art. 13(1)

Keyword:
Main request, auxiliary requests III, IV: inventive step (no)
Auxiliary request IA: admitted (no)
Auxiliary requests IB, II, V-VIII: added matter
Auxiliary requests IB, II: clarity (no)

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Case Number: T 1374/11 - 3.3.01

D E C I S I O N
of Technical Board of Appeal 3.3.01
of 11 March 2015

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Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 15 April 2011 concerning maintenance of the European Patent No. 1462101 in amended form.**

Composition of the Board:

Chairman	L. Bühler
Members:	L. Seymour
	G. Seufert

Summary of Facts and Submissions

I. European patent No. 1 462 101, was filed as application number 02 796 784.3, based on the international application published as WO 03/053430. The present appeal lies from the interlocutory decision of the opposition division maintaining the European patent in amended form, based on the third auxiliary request filed during oral proceedings before the opposition division, with the following claim 1:

"Use of ketoprofen for preparing a drinkable preparation comprising drinking water for animals or artificial milk for suckling animals supplemented with ketoprofen as an oral simultaneous coadjuvant treatment to antibacterial treatment of Porcine respiratory Disease Complex (PRDC) in a herd of pigs being antibacterially treated with enrofloxacin and Bovine Respiratory Disease (BRD) in a herd of calves being antibacterially treated with florfenicol,

in which the ketoprofen is previously dissolved in an aqueous solution, and in which this aqueous solution comprises a basic amino acid being L-arginine."

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

(4) WO 97/45113

(8) WO 96/16016

(11) F Longo et al., Proceedings 18th World Buiatrics Congress, Bologna, Italy, August 29 to September 2, 1994, 1343-1346

(14) L Reeve-Johnson, The Pig Journal, 1998, 42, 74-86

(26e) Lancement de Ketofen, L'action vétérinaire-LHV no 1212, 15.05.92

(41) C G MacAllister et al., JAVMA, 1993, 202(1), 71-77

(45) NOAH Veterinary Data Sheet Compendium 2000, entries for Ketofen 1%, Ketofen 10% and Ketofen Tablets

(48) P M Faulkner et al., J. Dairy Sci., 2000, 83, 2037-2041

III. In the decision under appeal, the subject-matter of claim 1 as granted was found to extended beyond the content of the application as originally filed (Article 100(c) EPC).

In its analysis of inventive step for the subject-matter of claim 1 of the first auxiliary request, the opposition division considered document (11) to represent the closest prior art, and defined the problem to be solved as lying in the provision of a system for a simultaneous coadjuvant treatment of a herd of animals with ketoprofen. The solution of simultaneous administration of ketoprofen via the drinking water or milk was considered to be obvious in view of the teaching of document (14). In addition, document (4) suggested that ketoprofen could be added to drinking water and given *ad libitum*. The patentee's argument that a prejudice had existed against the use of ketoprofen as claimed was rejected.

Regarding claim 1 of the second auxiliary request, the opposition division took the view that the additional

feature specifying the presence of L-arginine also could not establish an inventive step, in view *inter alia* of the disclosure of document (8).

Concerning claim 1 of the third auxiliary request (cf. above point I), the opposition division identified the examples as providing the basis for the subject-matter of claim 1. An inventive step was acknowledged in view of the evidence provided in the examples of the patent in suit, which demonstrated that the treatment as claimed was unexpectedly beneficial compared to the treatment with an antibacterial agent alone.

IV. The patentee and the opponent each lodged an appeal against this decision.

V. With its statement of grounds of appeal, the appellant patentee filed auxiliary requests I to VIII. With letter of 3 January 2012, these requests were renumbered as main request and auxiliary requests I to VII, respectively, and a new auxiliary request VIII was filed.

Claim 1 of the main request reads as follows:

"1. Use of ketoprofen for preparing a drinkable preparation comprising drinking water for animals or artificial milk for suckling animals supplemented with ketoprofen as an oral simultaneous coadjuvant treatment to antibacterial treatment of Porcine respiratory Disease Complex (PRDC) in a herd of pigs and Bovine Respiratory Disease (BRD) in a herd of calves."

Auxiliary requests I and II were subsequently replaced (see point VI below).

Claim 1 of auxiliary request III differs from that of main request in the insertion of the following feature at the end of the claim:

"in which the ketoprofen is previously dissolved in an aqueous solution, and in which this aqueous solution comprises a basic amino acid being selected from L-lysine and L-arginine".

Claim 1 of auxiliary request IV differs from claim 1 of auxiliary request III in the selection of L-arginine as basic amino acid.

Claim 1 of auxiliary request V differs from claim 1 of the auxiliary request maintained by the opposition division (cf. above point I) in that the basic amino acid is "selected from L-lysine and L-arginine".

Auxiliary request VI is identical to the auxiliary request maintained by the opposition division (cf. above point I).

Claim 1 of auxiliary request VII differs from claim 1 of the auxiliary request maintained by the opposition division (cf. above point I) in the replacement of the expressions "antibacterially treated with enrofloxacin" and "antibacterially treated with florfenicol" with "antibacterially treated **by injection** of enrofloxacin" and "antibacterially treated **by injection** of florfenicol", respectively (emphasis added).

Claim 1 of auxiliary request VIII differs from claim 1 of auxiliary request VII in that the herds are "antibacterially treated **by intramuscular injection**".

VI. Oral proceedings were held before the board on 11 March 2015.

Following the discussion on inventive step with respect to the main request, the appellant patentee replaced its previous auxiliary requests I and II (cf. above point V) with new auxiliary requests I and II. Subsequently, an additional auxiliary request was filed, numbered as "IA", and the auxiliary request I that had been submitted earlier was relabeled as "IB".

Auxiliary request IA consists of a single claim, which reads as follows (emphasis added):

"1. Use of **an aqueous solution of** ketoprofen for preparing **the herd's drinking water** supplemented with ketoprofen **in an amount ranging from 1 to 5 mg/day per kg in weight of the animals in the herd** as an oral simultaneous coadjuvant treatment to antibacterial treatment of Porcine respiratory Disease Complex (PRDC) in a herd of pigs and Bovine Respiratory Disease (BRD) in a herd of calves."

Claim 1 of auxiliary request IB differs from that of auxiliary request IA in the deletion of the feature "an aqueous solution of".

Claim 1 of auxiliary request II reads as follows (emphasis added):

"1. Use of ketoprofen for preparing a drinkable preparation comprising drinking water for animals supplemented with ketoprofen **in an amount ranging from 1 to 5 mg/day per kg in weight of the animals in the herd** as an oral simultaneous coadjuvant treatment to antibacterial treatment of Porcine respiratory Disease

Complex (PRDC) in a herd of pigs and Bovine Respiratory Disease (BRD) in a herd of calves, **wherein the animals receive drinking water ad-libitum.".**

VII. The appellant patentee's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

The subject-matter of claim 1 of the main request was based on the paragraphs on page 3, line 15 to page 4, line 21, and therefore conformed with Article 123(2) EPC. No disclosure could be found therein requiring the ketoprofen used to be present in aqueous solution.

Turning to the question of inventive step, the appellant patentee started from document (11) as closest prior art. This document taught the separate and individual treatment of groups of calves with the antibiotic spiramycin and the nonsteroidal anti-inflammatory drug (NSAID) ketoprofen, each administered by intramuscular injection. The problem to be solved in the light thereof was to be seen as lying in the provision of an improved way of toxicologically safely and simultaneously treating a herd of animals suffering from the respiratory diseases PRDC or BRD.

The solution proposed was characterised in the oral simultaneous treatment of the herd through a drinkable preparation supplemented with ketoprofen, offered *ad libitum*, that is, without consumption control. The latter feature was reflected in the wording of claim 1, through the juxtaposition of the features "simultaneous" and "herd".

Examples 2, 3 and 4 of the patent in suit demonstrated that this problem had been solved. In particular, said

coadjuvant treatment had been shown to speed up recovery with respect to herds receiving only antibacterial treatment. The improved weight gain disclosed in Example 3 was a clear indication of toxicological safety.

None of the cited prior art hinted at the claimed solution. In particular, the focus of document (14) was exclusively on antibacterial treatment through drinking water, and no useful teaching could be found with respect to other types of medication, such as ketoprofen. Indeed, a prejudice had existed against the solution proposed. Thus, the skilled veterinarian would have been well aware of the toxicological problems associated with the use of ketoprofen, and in particular of the high risk of gastrointestinal adverse events, as disclosed in document (45), and documents (26e) and (41). Moreover, it was known, for example from document (14), that strict dose control was not possible with medication provided in drinking water, owing to wide individual variation in drinking habits. Therefore, the skilled veterinarian would dismiss the possibility of *ad libitum* oral treatment with a drinkable ketoprofen preparation, for fear of producing gastrointestinal side effects, which would be detrimental to the overall aim of fattening the herd.

Documents (4) and (48) also did not suggest the claimed solution. Document (4) only disclosed ketoprofen as one example of the class of NSAIDs. Furthermore, the possibility of formulating the NSAID into a liquid preparation and blending this "with a liquid feed preparation or the animals' water supply" was only suggested in passing. Moreover, in Example 6 of document (4), ketoprofen had been applied to the feed of sows in a top dressing at an individually controlled

dose, and not administered *ad libitum*. Similarly, in document (48), the calves had been given ketoprofen individually in their milk rations. The disclosure of documents (4) and (48) would not therefore have dispelled any concerns of the skilled person with respect to the toxicological effects of *ad libitum* oral treatment with ketoprofen.

Accordingly, the skilled person would not have arrived at the claimed subject-matter without the exercise of inventive skill. The commercial success of the appellant patentee's product provided a further confirmation of inventive step.

Auxiliary requests IA, IB and II should be admitted into the proceedings. Auxiliary requests IB and II had been filed during oral proceedings before the board in direct response to the preceding discussions concerning the main request, with respect to the issues of claim construction, from which aspects had arisen that had not previously been discussed in any detail. Auxiliary request IA had been filed subsequently in order to address the appellant opponent's objections to auxiliary request IB.

The amendments to claim 1 of auxiliary request IB did not give rise to any formal objections under Articles 123(2) or 84 EPC. The basis in the application as originally filed for the claimed subject-matter could be found on page 2, lines 9 to 13, and page 4, lines 16 to 21, in combination with page 3, lines 25 to 35. Moreover, in the context of the claim, the feature "in an amount ranging from 1 to 5 mg/day per kg in weight of the animals in the herd" clearly referred to the amount of ketoprofen in the drinking water to be ingested.

Claim 1 of auxiliary request II was also in conformity with Articles 123(2) or 84 EPC. Support for the additional feature "wherein the animals receive drinking water ad-libitum" was derived from the reference in the paragraph on page 4, lines 16 to 21, to Examples 2, 3 and 4, which had the effect of transferring the complete disclosure of these examples into the general specification. Literal support in the description was therefore not required, since the feature "ad libitum" appearing in Example 2 was to be seen as forming part of the integral disclosure within the whole context of the specification.

Turning to the question of inventive step of auxiliary request III, the appellant patentee argued that an additional advantage of the treatment as defined in claim 1 was to be seen in the fact that the drinkable preparation was stabilised by salt formation with L-lysine or L-arginine. It had been demonstrated in Example 1 of the patent in suit that the corresponding aqueous solutions were highly compatible with different water qualities under field conditions. None of the cited prior art hinted at this solution to the problem posed. The documents cited by the appellant opponent, such as document (8), were silent as to the effect that further dilution with drinking water or artificial milk would have on the stability and solubility of ketoprofen compositions.

These submissions applied all the more to the subject-matter of claim 1 of auxiliary request IV, owing to the limitation to L-arginine, which was particularly preferred.

The remaining auxiliary requests were in conformity with Article 123(2) EPC: The subject-matter of claim 1 of auxiliary request V found its basis in the application as originally filed in claims 4, 8 and 9, in combination with the paragraph on page 4, lines 16 to 21. Through the reference in said paragraph to Examples 2, 3 and 4, the content of these examples had been incorporated into the general disclosure. Thus, the term "antibiotic treatment" appearing in said paragraph would be directly and unambiguously understood by the skilled reader to refer to a treatment with the specific exemplified antibiotics, namely, enrofloxacin for PRDC and florfenicol for BRD. The further limitation to L-arginine in claim 1 of auxiliary request VI was supported by the preferred embodiment according to page 5, lines 20 to 22, and by Examples 2, 3 and 4. Similarly, claims 1 of auxiliary requests VII and VIII more closely reflected the examples, through the limitation specifying that the antibacterial treatment was "by injection" and "by intramuscular injection", respectively.

VIII. The appellant opponent's arguments, insofar as they are relevant to the present decision, may be summarised as follows:

With respect to the subject-matter of claim 1 of the main request, the appellant opponent raised an objection under Article 123(2) EPC, arguing that it was evident from page 2, lines 9 to 13, and claim 4 of the application as originally filed that the disclosure was limited to the use of "an aqueous solution of ketoprofen" and not "ketoprofen" in general as claimed.

In its analysis of inventive step, the appellant opponent proposed several alternative closest prior art

documents, such as document (45), but agreed that document (11) represented a suitable starting point for analysing inventive step. No evidence had been provided that the use of oral ketoprofen in calves or pigs did not cause any gastrointestinal side effects, and no improvement in this respect had been demonstrated with respect to the coadjuvant treatment with ketoprofen according to document (11). Therefore, the problem to be solved could only be seen as lying in the provision of a more convenient coadjuvant treatment of a herd of animals suffering from the respiratory diseases PRDC or BRD.

The solution of administering ketoprofen to the herd through drinking water or artificial milk was obvious in view of the disclosure of document (14), which disclosed addition to drinking water as a preferred means of herd medication in response to an outbreak of respiratory disease. Given that aqueous solutions of ketoprofen were well known in the prior art, such as documents (26e), (41), (45) and (48), it would have been obvious for the skilled person to use ketoprofen in this form for preparing a drinkable preparation for the use as specified in claim 1.

None of the documents cited by the appellant patentee supported the assertion that a prejudice had existed regarding the use of ketoprofen in the veterinary field, but rather pointed to a favourable toxicity profile. In addition, documents (4) and (48) disclosed the oral administration of ketoprofen in pigs and calves, respectively. The extent of any gastrointestinal side effects would be dose-dependent, and the present claims were not limited to any specific dosages of ketoprofen. The appellant opponent disputed the appellant patentee's reading of claim 1 as implying an *ad libitum*

supply of the drinkable preparation; simultaneous provision of the herd with individual rations was not excluded. The appellant opponent further noted in this context that *ad libitum* supply of water could not be equated with *ad libitum* supply of ketoprofen. Although less control was possible in drinking water, a mean dose of ketoprofen, based on mean water consumption, would nevertheless be required, as had been exemplified in the patent in suit. Moreover, even were the appellant patentee's claim construction to be accepted, an inventive step could nevertheless not be acknowledged, since blending ketoprofen in the animals' water supply was specifically suggested in document (4).

The appellant opponent maintained that auxiliary requests IB and II should not be admitted, in view of their very late filing, during oral proceedings before the board. All the relevant arguments had been addressed in the decision under appeal. Therefore, appellant patentee should also have presented its complete case at the outset of the appeal proceedings, as required by the Rules of Procedure of the Boards of Appeal (RPBA). The appellant opponent further criticised the lack of clear allowability of these requests, and the fact that features had been introduced from the description. These objections applied all the more to auxiliary request IA, which had been filed at a yet more advanced stage of the oral proceedings before the board. The additional amendment to claim 1 of auxiliary request IA related to an objection that had been raised by the appellant opponent at the outset of oral proceedings. There could therefore be no excuse for the timing of its filing.

With respect to the amendments to claim 1 of auxiliary request IB, the appellant opponent raised a number of objections under Article 123(2) EPC. For example, the passage relied on by the appellant patentee, namely, page 2, lines 9 to 13, clearly referred to the use of "an aqueous solution of ketoprofen". Moreover, according to page 3 lines 31 to 35 of the application as originally filed, the dosage amount of "1-5 mg/kg/ day" was to be calculated based on the "weight of the live animal that ingests this drink preparation". These features were not reflected in claim 1 (Article 123(2) EPC). Furthermore, the requirements of Article 84 EPC were not met, since the meaning and point of reference of the newly introduced feature "in an amount ranging from 1 to 5 mg/day per kg in weight of the animals in the herd" was unclear. Analogous objections applied to claim 1 of auxiliary request II. The additional feature "wherein the animals receive drinking water ad-libitum" gave rise to a further objection under Article 123(2) EPC, since this feature had been extracted from a specific example.

With respect to auxiliary requests III and IV, the appellant opponent argued that the limitations introduced could not establish an inventive step. The only effect that had been disclosed in the patent in suit to result from the addition of a basic amino acid, such as L-arginine, was one of solubilisation. However, this property was well known in the prior art, as illustrated in document (8). The appellant patentee's argument regarding expected problems of stability and solubility on further dilution were merely unsubstantiated assertions. In fact, paragraph [0030] of the patent in suit confirmed that dilution facilitated solubilisation of ketoprofen.

The requirements of Article 123(2) EPC were not fulfilled for the subject-matter of the respective claims 1 of auxiliary requests V to VIII. The reference to "antibiotic treatment" in the paragraph on page 4, lines 16 to 21, pertained to the treatment as a whole. The extraction of particular features from the specific examples out of context amounted to an unallowable generalisation, for which no basis could be found in the application as originally filed.

IX. The appellant patentee requested that the decision under appeal be set aside and that the patent be maintained on the basis of:

- the main request filed as auxiliary request I with the statement of grounds of appeal dated 12 August 2011, or
- one of auxiliary requests IA, IB or II, filed during the oral proceedings on 11 March 2015, or
- one of auxiliary requests III to V, filed as auxiliary requests IV to VI, respectively, with the statement of grounds of appeal dated 12 August 2011,

- or, alternatively, that the appeal of the appellant opponent be dismissed (auxiliary request VI),
- or, alternatively, that the decision under appeal be set aside and that the patent be maintained on the basis of:

- auxiliary request VII, filed as auxiliary request VIII with the statement of grounds of appeal dated 12 August 2011, or
- auxiliary request VIII filed with letter of 3 January 2012.

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

X. At the end of the oral proceedings, the decision of the board was announced.

Reasons for the Decision

1. The appeals are admissible.

2. *Admissibility of auxiliary requests IA, IB and II* (Article 13(1) RPBA)

2.1 Auxiliary requests IB and II were submitted by the appellant patentee during oral proceedings before the board (cf. above point VI), immediately following discussions with respect to the main request regarding the question of whether the feature of *ad libitum* supply of the drinkable preparation was reflected in the wording of the claims. This issue only came into focus during oral proceedings before the board. Therefore, the board considered that the appellant patentee should, in the interest of procedural fairness, be given the opportunity to amend his claims accordingly.

Under these circumstances, the board decided to admit auxiliary requests IB and II into the proceedings.

2.2 Auxiliary request IA was subsequently submitted at a yet more advanced stage of oral proceedings, following discussions on the formal allowability of auxiliary requests IB and II. The amendment introduced into claim 1 of the newly filed request aimed at addressing an objection that had been raised by the appellant opponent at the outset of oral proceedings, namely,

regarding the fact that the paragraph on page 2, lines 9 to 13 of the application as originally filed specified that the ketoprofen used was in aqueous solution (cf. above point VIII, second paragraph). Therefore, if it had considered this to be necessary, the appellant patentee could and should have taken this objection into account when filing auxiliary request IB and II. The filing of auxiliary request IA cannot therefore be seen as a timely or appropriate reaction to developments during oral proceedings.

Consequently, the board decided not to admit auxiliary request IA into the appeal proceedings.

3. *Main request - Inventive step, claim 1 (Articles 52(1) and 56 EPC)*

3.1 Claim 1 of the main request (cf. above point V) has been worded as a "Swiss-type form" claim and relates to the use of ketoprofen for preparing a drinkable preparation comprising drinking water or artificial milk. The medical use thereof concerns the coadjuvant treatment to antibacterial treatment of porcine respiratory disease complex (PRDC) in a herd of pigs and bovine respiratory disease (BRD) in a herd of calves. The treatment of the herd is designated as being "oral simultaneous".

It was a matter of dispute between the parties how this claim should be construed. The appellant patentee argued that this was to be read as being limited to an *ad libitum* supply of the drinkable preparation to the herd as a whole. However, the board cannot accept that such a construction is supported by the wording of the claim. Thus, the term "oral simultaneous", when given its ordinary meaning in context in qualifying the

treatment of a herd, can only be understood as signifying that the members of the herd are treated by an oral administration route at the same time. This is consistent with the meaning attributed to the term "simultaneously" in conjunction with "herd" in the patent specification (see page 2, lines 26 to 31; page 3, lines 26 to 30). A simultaneous oral administration of the drinkable preparation as individual rations is therefore not excluded by the wording used.

3.2 The parties agreed that document (11) could be seen as constituting the closest prior art, and the board also considers that this document represents a suitable starting point for the assessment of inventive step.

Document (11) generally discusses the usefulness of nonsteroidal anti-inflammatory drugs (NSAIDs) as a complement to antibiotic therapy in the treatment of bovine respiratory diseases, and points to a previous study in which animals recovered more quickly after such a treatment, in comparison to antibiotic treatment alone (see pages 1344, 1345, sections entitled "Discussion"). In the field trial specifically reported in document (11), two groups of young cattle suffering from infectious enzootic bronchopneumonia were compared, one receiving antibiotic therapy with spiramycin alone, and the other additional adjunctive therapy with ketoprofen. The antibiotic was administered as two intramuscular (I.M.) injections at 48 hours interval, and ketoprofen as I.M. injections at dosages of 3 mg per kg on three consecutive days. Rectal temperatures were found to decrease significantly after each ketoprofen administration (see pages 1343, 1344, sections entitled "Enzootic

bronchopneumonia"). The following is concluded (see page 1345, "Conclusions"):

"Ketoprofen is doted with a powerful antipyretic property clearly demonstrated ... in field conditions of enzootic bronchopneumonia. Furthermore, this drug has potent anti-inflamatory effects and very low toxic potential. Those data may constitute a rational basis for the therapeutic use of ketoprofen as a complement to antibiotic therapy in the treatment of bovine respiratory diseases".

3.3 In view of the closest state of the art, it must now be determined which problem the claimed invention addresses and successfully solves.

The appellant patentee submitted a definition of the problem to be solved as lying in the provision of an improved way of toxicologically safely and simultaneously treating a herd of animals suffering from the respiratory diseases PRDC or BRD, and referred to the data in the patent in suit as demonstrating that this problem had been solved. However, the comparison provided therein is between the claimed treatment and a treatment with antibiotic alone, rather than the treatment disclosed in the closest prior art document (11). Therefore, there is no basis for assuming that the present treatment is in any way toxicologically safer than that disclosed in document (11). As is well established in the case law of the boards of appeal, alleged but unsupported advantage cannot be taken into consideration in respect of the determination of the problem to be solved.

Therefore, the problem to be solved in the light of the closest state of the art is defined in a less specific

manner, as lying in an improved coadjuvant treatment of a herd of animals suffering from the respiratory diseases PRDC or BRD.

3.4 The solution proposed in claim 1 relates to the oral simultaneous treatment of the herd through a drinkable ketoprofen preparation comprising drinking water or artificial milk.

Having regard to the experimental results reported in Examples 2, 3 and 4 of the patent in suit, the board is satisfied that the problem has been solved.

The improvement in the present treatment is seen as lying in the fact that "individual animals do not have to be held still to administer them the treatment, avoiding delays in administering the product and reducing manual labor costs and stress to animals" (cf. patent in suit, paragraph [0009], in combination with paragraphs [0004] and [0006]).

3.5 It remains to be investigated whether the proposed solution would have been obvious to the skilled person in the light of the prior art.

As set out above in point 3.2, document (11) discloses the use of ketoprofen in combination with an antibiotic for the treatment of BRD, whereby both active ingredients are administered by injection. This therapy is consistent with that indicated for cattle and pigs in the compendium cited as document (45), in the entry for "Ketofen 10%", which is an aqueous 10% solution of ketoprofen for parenteral administration.

The skilled veterinarian would certainly have been well aware of the inconvenience entailed in administering

medication by injection to herds of animals, as confirmed in documents (14) and (4) (see document (14), page 78, second complete paragraph, last sentence, and Table 2, first entry in the right-hand column; document (4), page 4, lines 9 to 11). In seeking a solution to the problem defined above, he would therefore have consulted further documents dealing with alternative modes of administration of the active ingredients used in the treatment according to document (11).

One such document is document (4). This document relates to methods for using NSAID compounds, in particular ketoprofen, for regulating the reproductive cycles of domesticated animals, most preferably pigs (see e.g. page 11, lines 8 to 12). The pharmacology of ketoprofen is discussed in detail (see page 6, line 30 to page 9, line 10, and page 13, line 10 to page 14, line 2), including its analgesic and antipyretic activity (page 13, lines 10 to 12). The NSAID compounds can be administered to the domesticated animals using a variety of conventional methods, for example, by oral or parenteral administration, most preferably orally in the form of a premix which is administered as a top dressing to the animal's normal feed (see page 15, line 7 to page 17, line 26; in particular page 15, lines 7 to 16 and page 17, lines 6 to 26). The latter mode of administration is exemplified in Example 6. Liquid preparations are also envisaged, including suspensions or solutions in aqueous or non-aqueous liquids (see page 15, lines 21 to 26). The liquid preparations can be applied to a solid feed, or "can be blended with a liquid feed preparation or the animals' water supply" (page 17, lines 17 to 26). Methods involving oral administration of the NSAID, and ketoprofen in particular, are disclosed on page 20,

lines 9 to 36. Hence, the skilled person would have derived the specific teaching from document (4) that ketoprofen, as an alternative to parenteral administration, can be orally administered to domestic animals, in particular pigs, including in the form of a liquid preparation added to a liquid feed preparation or the water supply.

The possibility of oral administration of ketoprofen in the form of a liquid preparation is also confirmed in document (48). The aim of this study was to assess the effectiveness of ketoprofen in decreasing the pain response in calves during the 24-hour period after hot-iron dehorning (page 2038, left-hand column, third complete paragraph). Liquid ketoprofen (10% Anafen; Rhône Mérieux Inc., USA) was provided orally in the milk rations on three occasions (page 2038, right-hand column, last complete paragraph), and was found to reduce behavioural evidence of pain compared to the control group (see Abstract).

It is therefore concluded that documents (4) and (48) suggest the suitability of liquid ketoprofen preparations for oral administration in both pigs and calves, including in "the animals' water supply" and milk rations. In view of the fact that the skilled person would readily identify this mode of medication as overcoming the above-mentioned disadvantages of the parenteral route (cf. document (14), page 78, third complete paragraph, and Table 2, first entries on pages 79 and 80), it would have been obvious for the skilled person, faced with the problem posed, to modify the process of document (11) accordingly.

Furthermore, the claimed requirement of simultaneity of the treatment, although not explicitly disclosed in

document (11), is considered to be a self-evident measure in view of the stated aim of document (11) in treating a group of animals under field conditions (see "Introduction").

It is therefore concluded that the skilled person would arrive at the subject-matter claimed, in both the embodiments of rationed individual supply and *ad libitum* shared supply (cf. above point 3.1), without the exercise of inventive skill.

3.6 The appellant patentee's submissions in favour of inventive step do not hold for the following reasons:

The main argument advanced was that a prejudice had existed that would have deterred the skilled person from arriving at the claimed solution.

The board notes in this context that, in the veterinary field, the modes of action and pharmacological effects of NSAIDs in general, and ketoprofen in particular, were well documented at the priority date of the patent in suit (see e.g. document (4), section 2.2; document (11), "Discussion"; document (26e), "Pharmacologie"; document (41), first four paragraphs of introduction on pages 71, 72; document (45), entry "Ketofen 10%", "Uses"; document (48), "Abstract", last sentence), as summarised in document (41) as follows (see page 71, paragraph bridging left- and right-hand columns):

"The NSAID are a diverse group of compounds that are antipyretic, anti-inflammatory, and analgesic agents. They share a basic mechanism of inhibiting cyclooxygenase, resulting in decreased production of prostaglandin."

The potential for adverse side-effects of this class of drugs, such as gastrointestinal toxicity, was also widely reported (see e.g. document (4), section 2.2, last two paragraphs; document (26e), "Tolérance"; document (41), page 72, first complete paragraph; document (45), entry "Ketofen 10%", "Contra-indications, warnings etc" and "Further Information").

However, ketoprofen was also disclosed to be well tolerated in veterinary use, including in pigs, cattle, horses, dogs and cats. For example, document (41) reports a comparative study into the toxicity of three NSAIDs, and concludes that "Under the conditions of this study and with total daily doses that exceeded the manufacturers' recommended doses, the toxic potential ... was ... least for ketoprofen in clinically normal adult horses" (see page 71, "Summary", last six lines). Document (26e), which relates to the launch of an injectable 10% ketoprofen solution for cattle, dogs and cats, discloses that, at eight times manufacturers' recommended doses, general toxicity was not observed (left-hand column, last paragraph). Similarly, in document (45) the following is stated (entry "Ketofen 10%", "Further Information"):

" Ketoprofen is simlarly well tolerated in cattle, where doses of up to 15 mg/kg/day (5 times the recommended dose) for 5 consecutive days have been given without significant adverse effects. The product has been safely given to calves as young as 3 days of age, and to pregnant and lactating cattle.

Ketoprofen is well tolerated in pigs. Doses of 9 mg/kg/day (3 times the recommended dose) for 3 consecutive days have been given with no adverse effects."

More particularly, as outlined above in point 3.5, documents (4) and (48) specifically disclose the oral use of ketoprofen in groups of pigs and cattle, in daily dosages similar to those suggested in the patent in suit (cf. paragraph [0017], with e.g. document (4), Example 6 and document (48), page 2038, right-hand column, last complete paragraph). In view of these disclosures, there can be no question of a prejudice against the use of ketoprofen in the present setting.

The appellant patentee more specifically argued that there would be a prejudice against an *ad libitum* supply of the drinkable preparation. Although it is not accepted that this feature is reflected in the wording of claim 1 (cf. above point 3.1), the board nevertheless wishes to note that a prejudice can also not be recognised for this embodiment. In this case too, the appellant patentee acknowledged that control of daily dosage would be necessary based on average intake (cf. patent in suit, paragraphs [0061] and [0080]). Although an *ad libitum* supply raises issues of variable individual intake (see document (14), Table 2, pages 79 and 80, right-hand column), no reasons were given as to why the skilled person would assume that the extent of any variability would be such as to result in toxic doses that would preclude administration in this manner.

Indeed, it can also be derived from document (4) that such a prejudice did not exist, since it is specifically foreseen therein that liquid preparations "can be blended with ... the animals' water supply" (page 17, lines 24 to 26). The submission of the appellant patentee that this disclosure would be disregarded by the skilled person as being only mentioned in passing is not considered to be

persuasive, in view of the fact that it appears in a short paragraph relating to liquid oral preparations, which are offered as an alternative to the most preferred embodiment of specific solid oral preparations (see page 17, lines 6 to 26). There would therefore be no reason for the skilled person to ignore this suggestion as lacking in substance.

Concerning the disclosure of document (14), it is noted that although its focus is on treatment of pig herds with antibiotics, the teaching thereof is by no means restricted to such medication (see, for example, title and first sentences of summary). In particular, in the section entitled "Ease of administration" (pages 78 to 80), reference is generally made to "a chemotherapeutic" and "delivery strategies for chemotherapy", and the skilled person would readily recognise the advantages and disadvantages disclosed therein to be applicable to medication other than antibiotic treatment.

Finally, in the present case, the claimed solution was found not to be inventive based on technical analysis of the cited prior art, in accordance with the problem-solution approach. Under these circumstances, a mere allegation of commercial success, wich may equally depend on extraneous factors, such as marketing, cannot alter the board's finding.

3.7 Consequently, the main request is rejected for lack of inventive step of the subject-matter of claim 1.

4. *Auxiliary request IB - claim 1, Articles 123(2), 84 EPC*

4.1 The application as originally filed as referred to herein designates the English translation of the

international application originally filed in Spanish, submitted on 8 July 2003 on entry into the regional phase before the EPO, as later corrected with letter of 17 April 2006.

4.2 In order to assist the analysis as to whether the requirements of Article 123(2) EPC have been met in the present case, the passages cited by the appellant patentee are reproduced as follows (emphasis added):

4.2.1 "The solution provided by the invention is based on the inventor's observation that by adding **an aqueous solution of ketoprofen to a herd's drinking water** or to the artificial milk for suckling animals in an appropriate amount relative to animal's bodyweight and the number of animals present, a herd of animals can be easily treated simultaneously" (page 2, lines 9 to 13).

4.2.2 "Since the drink preparation of the invention is designed to treat a herd of animals, the amount of ketoprofen contained in said drink preparation can vary within a wide interval. In general, the drink preparation of the invention contains ketoprofen in an amount sufficient to provide a therapeutically effective amount to **the animal that ingests this drink preparation**. As used in this specification, the term "therapeutically effective amount" refers to an amount sufficient to have a therapeutic effect on the animal, for example, **an amount ranging from 1 to 5 mg of ketoprofen per kg in weight of the live animal that ingests this drink preparation per day (1-5 mg/kg/ day)**" (page 3, lines 25 to 35).

4.2.3 "Examples 2 and 3 demonstrate the clinical efficacy of a drink preparation of the invention as a coadjuvant treatment to **the antibiotic treatment** of Bovine

Respiratory Disease (BRD) in herds of calves or suckling calves. Example 4 illustrates the clinical efficacy of a drink preparation of the invention as a coadjuvant treatment to **the antibiotic treatment** of Porcine Respiratory Disease Complex (PRDC) in herds of fattening pigs" (page 4, lines 16 to 21).

4.3 It is immediately evident from a comparison of claim 1 of auxiliary request IB and the first passage reproduced above that the feature requiring that the ketoprofen used to be in "an aqueous solution" is missing from said claim, contrary to Article 123(2) EPC.

Moreover, according to the second passage reproduced above, the "amount ranging from 1 to 5 mg/day per kg" relates to the "weight of the live animal that ingests this drink preparation". These features are not reflected in present claim 1. More specifically, it is clear from said passage that it is the dosage administered that is being defined, which is part of the definition treatment. In contrast, in the present claim, the feature "in an amount ranging from 1 to 5 mg/day per kg in weight of the animals in the herd" has been inserted in the part of the claim defining the manufacture of the composition to be administered, and the reference to ingestion by the animal has been omitted. Therefore, said feature defines an absolute amount in the herd's drinking water, in terms of extraneous factors relating to the treatment. Such a definition is neither supported by the application as originally filed, nor does it allow a clear conclusion as to what is intended to be claimed (Articles 123(2), 84 EPC).

In view of the above considerations, it is concluded that claim 1 of auxiliary request 1 does not fulfil the requirements of Articles 123(2) and 84 EPC.

5. *Auxiliary request II - claim 1, Articles 123(2), 84 EPC*

5.1 The considerations concerning claim 1 of the auxiliary request IB, as set out above in the second paragraph of point 4.3, apply equally to claim 1 of auxiliary request II, in view of the fact that the same feature relating to dosage is inserted at the same position of the claim.

5.2 In addition, the feature "wherein the animals receive drinking water ad-libitum" is considered to give rise to a further objection under Article 123(2) EPC.

The only disclosure of this feature in the application as originally filed is in Example 2, on page 12, lines 18 to 20, embedded in a very detailed and specific description of a study entitled "Study of the clinical efficacy of an aqueous solution of ketoprofen, administered orally in drinking water, as a complement to the antibiotic treatment of respiratory disease in calves". Similar wording is used in the paragraph referring to this example on page 4, lines 16 to 21, as reproduced above in point 4.2.3.

The information that the skilled person directly and unambiguously derives from these passages is that said example as a whole illustrates the general concept of coadjuvant treatment as set out above. In the general part of the description, it is merely disclosed that the amount that the animal's consumption of water is a very variable factor (see e.g. page 4, lines 30 to 33) However, no pointer can be found in the application as

originally filed that the feature of *ad libitum* supply of the drinkable preparation is to be singled out from Example 2 as a preferred feature and combined within a more general context disclosed elsewhere. Therefore, it is concluded that the combination of features now claimed does not directly and unambiguously emerge from the application as originally filed as a preferred embodiment.

The board agrees with the appellant patentee that the examples are an integral part of the application as originally filed. However, this does not mean that they can be seen as a reservoir, which can be dismantled at will to create any number of distinct embodiments.

5.3 Consequently, the subject-matter of claim 1 of auxiliary request II also does not meet the requirements of Article 123(2) EPC.

6. *Auxiliary request III – Inventive step, claim 1 (Articles 52(1) and 56 EPC)*

In comparison with claim 1 of the main request, claim 1 of auxiliary request III is characterised by the addition of the feature "in which the ketoprofen is previously dissolved in an aqueous solution, and in which this aqueous solution comprises a basic amino acid being selected from L-lysine and L-arginine" (cf. above point V).

The appellant patentee argued that the solution to the problem posed was now additionally characterised in that the drinkable preparation was stabilised by salt formation with L-lysine or L-arginine, and that this additional improvement could not have been predicted from the prior art.

However, the board cannot accept that the improvement in stability relied on by the appellant has been demonstrated. The stability studies on further dilution in drinking water and in artificial milk, as set out in Example 1 of the patent in suit (paragraph [0041]) were performed on a single composition ("EV solution", page 6, lines 1 to 9), and the results obtained are not comparative and can only be attributed to the composition as a whole, rather than any particular component therein.

The only role attributed to L-lysine and L-arginine in the patent in suit is the solubilisation of ketoprofen (cf. paragraphs [0022], [0024] and [0040]). However, this property is already suggested in the prior art, such as document (8). In the paragraph bridging pages 1 and 2 of this document, the poor solubility of ketoprofen is highlighted, and the fact that this drawback "makes both the parenteral and oral administrations difficult". As a solution to this problem, document (8) suggests formation of salts that are highly soluble in water (see sentence bridging pages 2 and 3), whereby L-lysine and L-arginine are listed as preferred salt formers (page 4, lines 21 to 24).

The appellant patentee argued that this document was silent as to the effect that further dilution with drinking water or artificial milk would have on the stability and solubility of ketoprofen, but did not substantiate why any problems were to be expected in this regard. Indeed, the patent in suit rather indicates that "solubilization of ketoprofen is aided by diluting the product" (paragraph [0030]).

Consequently, the use of L-lysine and L-arginine to solubilise ketoprofen is considered to be an obvious additional measure as a solution to the problem posed (cf. above point 3.3, last paragraph).

In view of the above additional considerations, in combination with the analysis provided above in point 3.5, auxiliary request III is rejected for lack of inventive step of the subject-matter of claim 1.

7. *Auxiliary request IV - Inventive step, claim 1 (Articles 52(1) and 56 EPC)*

Present claim 1 differs from that of auxiliary request III in the limitation to the preferred basic amino acid L-arginine. However, this amendment does not alter the assessment presented above in point 6. Consequently, auxiliary request IV is also rejected for lack of inventive step of claim 1.

8. *Auxiliary requests V to VIII - respective claims 1, Article 123(2) EPC*

8.1 In claim 1 of auxiliary request V, the antibiotics used have been specified to be enrofloxacin for PRDC and florfenicol for BRD. The only disclosure of these specific active ingredients in the application as originally filed is in Examples 2 to 4 (page 14, lines 22 to 27; page 20, lines 5 to 9; page 25, lines 2 to 8). However, in these examples, the antibiotics used are only one of many features detailed for the studies disclosed, and a similar reasoning applies to that discussed above in point 5.2 for the feature "wherein the animals receive drinking water ad-libitum". Again, features have been arbitrarily isolated from their context in the examples, and combined with further

features from other parts of the application, so as to create a combination of features that was not directly and unambiguously derivable from the application as originally filed.

In this context, the appellant patentee argued that the term "the antibiotic treatment" appearing in the paragraph reproduced above in point 4.2.3 would be directly and unambiguously understood to refer to a treatment with the specific exemplified antibiotics. However, as set out in the application as originally filed, in the sections of the examples entitled "Treatments" (see Examples 2 and 3, sections 1.3; Example 4, section 1.2), this term is characterised not only by the specific active ingredients, but also by the nature of the corresponding compositions, and the dose, therapeutic regime and route of administration.

Accordingly, it must be concluded that no direct and unambiguous basis can be found in the application as originally filed for the selection and combination of features now claimed in claim 1.

8.2 With respect to auxiliary requests VI to VIII, the appellant patentee did not advance any additional arguments pursuant to Article 123(2) EPC, apart from the fact that the respective claims 1 were formulated to be closer to the examples.

However, in view of the fact that the features chosen still only represent further arbitrary selections from those exemplified, the assessment presented above in point 8.1 applies to these requests *mutatis mutandis*.

8.3 Consequently, the subject-matter of the respective claims 1 of auxiliary requests V to VIII does not meet the requirements of Article 123(2) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairman:

M. Schalow L. Bühler

Decision electronically authenticated