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Datasheet for the decision of 21 July 2016

Case Number: T 1270/12 - 3.3.08

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Language of the proceedings: EN

Title of invention:

LAWSONIA INTRACELLULARIS CULTIVATION, ANTI-LAWSONIA INTRACELLULARIS VACCINES AND DIAGNOSTIC AGENTS

Patent Proprietor:

BOEHRINGER INGELHEIM VETMEDICA, INC.

Opponents:

Akzo Nobel N.V.
Wyeth LLC

Headword:

Lawsonia intracellularis cultivation vaccine infection rate/ BOEHRINGER INGELHEIM

Relevant legal provisions:

EPC Art. 83, 56
RPBA Art. 13(1)

Keyword:

Main Request, Auxiliary Requests I-IV; admissibility (yes)
Main Request, Auxiliary Requests I-III; sufficiency disclosure (no)
Auxiliary Request IV; meets all requirements of the EPC (yes)

Decisions cited:

G 0001/03, T 0051/08, T 0692/08, T 1846/10, T 0790/10, T 1155/13

Catchword:

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Case Number: T 1270/12 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 21 July 2016

Appellant: (Opponent)	Wyeth LLC Five Giralda Farms Madison, NJ 07940 (US)
Representative:	Mannion, Sally Kim Zoetis UK Limited Walton Oaks Dorking Road Tadworth Surrey KT20 7NS (GB)
Respondent: (Patent Proprietor)	BOEHRINGER INGELHEIM VETMEDICA, INC. 1568 North Main Avenue Siuox Center, IA 51250-0050 (US)
Representative:	Vossius & Partner Patentanwälte Rechtsanwälte mbB Siebertstrasse 3 81675 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 5 April 2012 concerning maintenance of the European Patent No. 0843818 in amended form.**

Composition of the Board:

Chairman	M. Wieser
Members:	P. Julià
	D. Rogers

Summary of Facts and Submissions

I. European patent no. 0 843 818 was granted with 23 claims on the basis of European patent application no. 96 921 391.7. Two oppositions were filed under Articles 100(a), (b) and (c) EPC. The opposition division rejected the oppositions and both opponents filed an appeal. In decision T 692/08 of 10 February 2010, this board in a different composition decided that the Main Request before it fulfilled the requirements of Articles 123(2),(3) and 84 EPC and remitted the case to the opposition division for further prosecution. The opposition division decided to maintain the patent on the basis of a Main Request filed at oral proceedings held on 14 December 2011.

II. Again, both opponents filed an appeal. With their respective statements setting out the Grounds of Appeal, they submitted new evidence.

III. In reply thereto, the patentee (respondent) filed a new Main Request and new Auxiliary Requests I to X, together with new evidence.

IV. Further submissions were filed by opponent 01.

V. The parties were summoned to oral proceedings. In a communication pursuant to Article 15(1) of the Rules of Procedure of the Boards of Appeal (RPBA), they were informed of the board's preliminary, non-binding opinion on some issues of the case.

VI. On 7 June 2016, opponent 01 withdrew its opposition and is, therefore, no longer a party to the proceedings.

VII. On 6 July 2016, opponent 02, the sole remaining appellant (hereinafter "*the appellant*") informed the board, without filing substantive arguments, that it would not attend the oral proceedings.

VIII. In reply to the board's communication, the respondent submitted substantive arguments and filed a new Main Request, new Auxiliary Requests I to VIII and Exhibits 1 and 2.

IX. Oral proceedings were held on 21 July 2016 in the absence of the appellant.

X. Claim 1 of the **Main Request** and of **Auxiliary Requests I and III** reads as follows:

"1. A method for cultivating *L. intracellularis* bacteria comprising obtaining culture cells infected with *L. intracellularis*, incubating said infected cells at an oxygen concentration of less than about 18 percent while maintaining said infected cells in suspension, wherein harvesting is done when greater than about 70% of the cells as determined by the IFA method are infected."

XI. Claims 1, 11 and 13 of **Auxiliary Request II** read as follows:

"1. A method for cultivating *L. intracellularis* bacteria comprising obtaining McCoys cells infected with *L. intracellularis*, incubating said infected McCoys cells at an oxygen concentration of less than about 18 percent while maintaining said infected McCoys cells in suspension, wherein harvesting is done when greater than about 70% of the cells as determined by the IFA method are infected.

11. *L. intracellularis* bacteria deposited as ATCC 55783.

13. A method for producing an attenuated *L. intracellularis* strain comprising obtaining culture cells infected with *L. intracellularis* bacteria, incubating said infected cells at an oxygen concentration of 0 percent to about 18 precent, agitating said infected cells so as to cultivate said bacteria while maintaining said infected cells in suspension, passaging at least a portion of said cultivated bacteria, harvesting at least a portion of said cultivated bacteria, and selecting for an attenuated strain to provide an attenuated *L. intracellularis* bacteria."

Claims 2-10 and claims 14-20 were directed to preferred embodiments of claims 1 and claim 13, respectively. Claim 12 was directed to a method for cultivating *L. intracellularis* bacteria using McCoys cells and having essentially the technical features of claim 1.

XII. **Auxiliary Request IV** is identical to Auxiliary Request II but for the deletion of claims 13-20.

XIII. The following documents are referred to in this decision:

D3: S. McOrist *et al.*, Res. Veterinary Sci., 1995, Vol. 95, pages 255 to 260;

D4: S. McOrist *et al.*, Infection and Immunity, October 1993, Vol. 61, No. 10, pages 4286 - 4292;

D5: G.H.K. Lawson *et al.*, J. Clin. Microbiol.,

May 1993, Vol. 31, No. 5, pages 1136 - 1142;

D6: J.E.Tam *et al.*, BioTechniques, 1992, Vol. 13, No. 3, pages 374, 376 and 378;

D91/D91a: Experimental data signed on 27 September 2011 by Dr J. Kroll;

D97: Declaration of Dr S. McOrist signed on 13 October 2011.

XIV. The submissions of the appellant made in writing, insofar as they are relevant to the present decision, may be summarized as follows:

Main Request, Auxiliary Requests I and III
Article 100(b) EPC (Article 83 EPC)
Claim 1

The nature and type of the infected host cell and the conditions of the cell culture were essential features of the method of claim 1. Evidence on file showed important differences in the cell infection rate among different host cells (50%/100% infection for IEC-18/ McCoy cells, respectively) and between host cells grown in monolayer or in suspension (2.9%/50%, respectively, for IEC-18 cells) (D91/D91a, D97). There was no evidence showing that the feature "*greater than about 70% of the cells ... are infected*" was achieved in any of the Examples of the patent. The patent did not support this feature and did not teach how to predictably achieve an infection level of greater than 70% over lower levels of infection. There was no certainty in achieving the feature required by claim 1 since a balance was required between the number of infected cells and their lysis. In the patent, a 100%

infection was achieved only with a suspension of McCoy cells grown on microcarriers but the patent failed to disclose how to achieve such a balance under all other possible conditions.

Auxiliary Request II
Article 100(b) EPC (Article 83 EPC)
Claim 13

The patent did not disclose the technical features that would allow a skilled person to produce an attenuated *L. intracellularis* strain (the specific *L. intracellularis* strain used, the nature of the infected cells and the level of passaging required for attenuation, the culture conditions and the means of testing for an attenuated strain, etc.). This had the consequence that the actual working of the invention was not within the routine skill of a person skilled in the art. Reference was made to the submissions filed in the parallel divisional application underlying decision T 1846/10 of 12 March 2015, in particular with regard to the concept of attenuating a pathogenic microorganism for obtaining a strain suitable for use as a vaccine. The appellant and respondent were both parties to case T 1846/10. In T 1846/10, the board found that claim 12 of the Main Request, directed to a method for producing a live vaccine comprising an attenuated *L. intracellularis* strain, did not satisfy the requirements of Article 83 EPC.

Auxiliary Request IV
Article 100(b) EPC (Article 83 EPC)
Claim 1

There were important differences between cell cultures in free suspensions (with no adherence to any solid

surface) and in fixed suspensions (with particles, microcarriers, etc.). The patent referred to a rate of 100% infection achieved with a suspension of McCoy cells grown on microcarriers but not in free suspension (Example 3 of the patent). The patent contained no evidence that free floating McCoy cells (without microcarriers) could be used for culturing *L. intracellularis* in suspension. Indeed, at the priority date, it was commonly understood, and evidence in this respect was on file, that McCoy cells were anchorage-dependent cells that could not be cultivated in the absence of a solid support.

Article 100(a) EPC (Article 56 EPC)
Claims 1-10 and 12

The closest prior art document D5 disclosed the culture of *L. intracellularis* bacteria in cell monolayers. The technical problem to be solved was the provision of an improved culture method for *L. intracellularis*. In order to solve this problem, the common general knowledge available to a person skilled in the art of cell cultivation would have suggested to scale-up the cultivation system disclosed in document D5, to increase thereby the number of infected host cells and to achieve a greater yield of bacteria. This scale-up step would have merely required the use of a greater surface area on which the infected host cells were grown. As shown by prior art on file (*inter alia*, document D6), it was well-known to scale-up monolayer cultures of anchorage-dependent cells by using microcarriers, beads or the like.

In decision T 692/08 (*supra*), the board held that the use of the suspension culture technique alone was not inventive. The feature introduced into claim 1 for

providing an inventive contribution, namely to harvest the host cells "*when greater than about 70%*" were infected, resulted only from the application of obvious measures. The percentage of 70% infection was automatically achieved by a skilled person when performing an obvious suspension culture. It was a mere "*bonus*" effect which, according to the established case law, could not form a basis for an inventive step. Moreover, claim 1 did not comprise all essential features (culture conditions, presence of microcarriers, etc.) necessary to achieve an improved cultivation method. There was no evidence in the patent that the problem was solved over the entire scope of the claim.

Claim 11

The closest prior art, document D4, described the passaging of cells infected with *L. intracellularis* and the testing of various inocula from different passages in pigs. The pigs receiving inocula of 13 week passage showed only minor lesions compared to inocula of lower passage. It was stated in document D4 that attenuation of the *L. intracellularis* bacteria was the likely cause of the reduction in lesions. Thus, document D4 taught the skilled person that *L. intracellularis* was attenuated upon repeated passaging or subculturing, as was already known from other unrelated intracellular organisms. Starting from this prior art, the technical problem to be solved was the provision of an improved method of producing attenuated strains of *L. intracellularis,* the strains produced thereby being suitable for use in a vaccine against *L. intracellularis*. The claimed method and the resulting attenuated strains were obvious. Indeed, a skilled person knowing document D4 would have sought to extend

the cultivation method disclosed therein by passaging and selecting for an attenuated strain suitable for a vaccine. The deposited attenuated *L. intracellularis* strain of the patent was not associated with any advantage that could form the basis for an inventive step.

XV. The submissions of the respondent, insofar as they are relevant to the present decision, may be summarized as follows:

Main Request, Auxiliary Requests I and III
Article 100(b) EPC (Article 83 EPC)
Claim 1

The skilled person would not seriously contemplate far from ideal conditions when intending to achieve the feature "*greater than about 70%*" infection. The patent provided ample teaching for achieving this feature. Evidence on file showed that, after one week of culture in suspension, the infection rates were 50% for IEC-18 and 100% for McCoy cells (documents D91/D91a). As explained in document D97, an infection rate greater than 70% would have been achieved for IEC-18 cells after slightly longer cultivation time. Both, IEC-18 and McCoy cells were described in the patent as preferred cell lines for carrying out the disclosed culture method. Indeed, the host cells used were not a crucial factor for achieving a high infection rate. The different results obtained by using different available cell types did not cast serious doubt on the workability of the invention over the entire scope of the claim. There was no evidence on file to substantiate the appellant's line of argument.

Auxiliary Request II

Article 100(b) EPC (Article 83 EPC)
Claim 13

In reply to the Grounds of Appeal, the respondent argued that the subject-matter of claim 13 defined a method for the development of an attenuated vaccine against *L. intracellularis* by referring to the three features characterizing attenuated bacteria suitable as live vaccines (apathogenicity, suitable remaining immunogenicity, and genetic stability). At the oral proceedings, the respondent stated again that the subject-matter of claim 13 of Auxiliary Request II was directed to a method for producing an attenuated vaccine and drew the board's attention to the reasoning given in decision T 1846/10 (*supra*). It argued that the board's finding in this case that claim 12 of the Main Request did not meet the requirements of Article 83 EPC was incorrect. In this respect, the respondent also wanted to introduce a further declaration of a technical expert.

The respondent argued that the board in the present case should not apply the *res judicata* doctrine, and hence should not follow the decision of the board in T 1846/10. The claims in the present case and in the case underlying decision T 1846/10 were different. There was also different prior art and evidence on file and the description of the patent differed from the description of the divisional patent underlying decision T 1846/10.

Auxiliary Request IV
Article 100(b) EPC (Article 83 EPC)
Claim 1

The validity of the experimental evidence allegedly showing that McCoy cells could not be cultured in free suspensions was doubtful. In fact, the feature "*greater than 70%*" infection excluded from claim 1 all culture methods run under sub-optimal conditions, such as those obviously used in this evidence. Moreover, this evidence had been filed in the present case with the appellant's Grounds of Appeal as document D92. However, in the case underlying the decision T 692/08 (*supra*), this evidence was late filed, shortly before the oral proceedings before the board. Neither at these oral proceedings nor at any other point had a decision as to its admissibility been taken.

Article 100(a) EPC (Article 56 EPC)
Claims 1-10 and 12

The closest prior art document D5 described the cultivation of *L. intracellularis* in monolayer cultures of IEC-18 cells. The maximum infection rate was 6.29% (5 days post infection; (p.i.)) for IEC-18 cells exposed to an isolate derived from intestine and 20% (7-9 days p.i.) for IEC-18 cells exposed to supernatant fluid from infected IEC-18 cell cultures. Hence, the claimed subject-matter differed from document D5 in that the infected cells were McCoy cells, which were maintained in suspension and which were harvested when more than about 70% were infected. The technical problem to be solved was the provision of an improved method for cultivating *L. intracellularis*. The claimed subject-matter solved this problem. Documents D91/D91a and D97 reported an infection rate of 100% (7 days p.i.) in suspension cultures of McCoy cells.

The various differences between *L. intracellularis* and other obligate intracellular bacteria for which

suspension culture had been established, such as *Chlamydia* (*inter alia* document D6), made it impossible to extrapolate from the results described in the prior art. The specific growth requirements of *L. intracellularis* known from the prior art (*inter alia* documents D4, D5) would have led the skilled person to expect that this organism required growth conditions mimicking the conditions found in its natural habitat, i.e. the intestine epithelium. The skilled person had no reason to turn away from the well-known static monolayer culture of intestinal epidermal cells described in the prior art. Moreover, on the basis of studies with other obligate intracellular bacterial parasites, such as *Chlamydia* (*inter alia* document D6), a person skilled in the art would have expected comparable infection rates for *L. intracellularis* cultivated in monolayer (not exceeding 20%) and in suspension cultures. It was thus surprising to find that cultivation of *L. intracellularis* in suspension resulted in an increased infection rate, as described in the patent and proven in documents D91/D91a and D97. The case law on *"bonus effects"* related to cases where the surprise resulted from the achievement of an unexpected quantity of a known effect, not to cases where the effect *per se* was completely unexpected. In the present case, there was no expectation at all that a high infection rate could be obtained by cultivating the infected host cells in suspension instead of monolayers. Thus, the case law referred to by the appellant did not apply.

Claim 11

The closest prior art document D4 showed that *L. intracellularis* isolated from pigs with porcine proliferative enteropathy (PPE), cultivated and

passaged on IEC-18 cell monolayers, were capable of reproducing PPE in infected pigs. The technical problem to be solved was the provision of an attenuated *L. intracellularis* for the development of a vaccine. It could not be expected that a pathogenic bacterium would automatically become an attenuated live vaccine by simply cultivating and passaging it long enough. Document D4 did not disclose the attenuation of *L. intracellularis* by passaging. As it was derivable from the results reported in Tables 1 and 2 of this document, the development of pathologic lesions was dose-dependent and did not correlate with the number of passages of the cells. Document D4 disclosed a "*dosage depending effect*" and not a "*passage attenuation effect*". None of the strains disclosed in this document had the advantageous properties of the *L. intracellularis* bacteria deposited as ATCC 55783 nor could the existence of such a strain be reasonably expected from the teaching of document D4.

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

XVII. The respondent (patentee) requested that the appeal be dismissed or, alternatively, that the decision under appeal be set aside and the patent be maintained upon the basis of the claims of one of the Auxiliary Requests I to IV, all filed under cover of a letter dated 14 July 2016.

Reasons for the Decision

Scope of the appeal proceedings

1. The decision under appeal is concerned with Articles 56 and 83 EPC only. In the decision T 692/08, this board,

in a different composition decided that the Main Request fulfilled the requirements of Articles 123(2), (3) and 84 EPC (cf. T 692/08, *supra*, point 9 of the Reasons). Novelty was not challenged in opposition proceedings (cf. page 3, point 14 of the decision under appeal).

Admissibility of new evidence

2. Documents D1-D37 were filed at the beginning of the opposition proceedings, documents D38-D91 were filed during the first appeal proceedings (cf. T 692/08, *supra*). Documents D91a-D97 were filed after the board remitted the case to the opposition division and documents D98-D106 have been filed during the present second appeal proceedings.

3. There is no indication on file that documents D1-D91 have not been admitted into the proceedings. Moreover, none of the parties has objected to the admissibility of any of the documents filed during the second opposition and the present second appeal proceedings. Therefore, the board does not consider it necessary to enter into a detailed discussion on the admissibility of any evidence on file.

4. However, this does not apply to the experimental data submitted by former opponent 01 with the statement setting out its Grounds of Appeal (cited therein as document D92). The admissibility of this data, which has been disputed by the respondent, is examined by the board in the section below, dealing with the requirements of Article 83 EPC with regard to Auxiliary Request IV.

Admissibility of the Main Request and Auxiliary Requests I-IV

5. In reply to the Grounds of Appeal, the respondent filed a Main Request which it considered to be identical to the request upheld by the opposition division. However, the new Main Request actually differed from this request in claim 13 where one of the deposited strains had been deleted. In reply to the board's communication pointing at this difference, the respondent corrected the request and filed a Main Request identical to the request upheld by the opposition division, which does not have to be examined as to its admissibility.

6. The amendments introduced into Auxiliary Requests I-IV consist of a deletion of claimed subject-matter (a deposited strain in all Auxiliary Requests and the method for producing attenuated *L. intracellularis* in Auxiliary Requests III-IV) and of a limitation of the scope of the claims by introduction of subject-matter of a dependent claim (infected host cells limited to McCoy cells in Auxiliary Requests II and IV). They are straightforward in nature, do not raise any new issues and have been made in direct reply to the board's communication pursuant to Article 15(1) RPBA.

7. Therefore, the board, exercising its discretion under Article 13(1) RPBA, decides to admit Auxiliary Requests I-IV into the procedure.

Main Request, Auxiliary Requests I and III
Article 100(b) EPC; Article 83 EPC
Claim 1

8. Claim 1 of these requests is identical and relates to "*a method for cultivating L. intracellularis bacteria comprising obtaining culture cells infected with L. intracellularis*", without containing any limitation to

the type and nature of the infected host cells. The claim further requires to maintain "*said infected cells in suspension*" and that the "*harvesting is done when greater than about 70% of the cells ... are infected*" (cf. point X *supra*). Whether the claimed method is disclosed in a way that enables a skilled person to achieve an infection rate greater than 70% has to be examined under Article 83 EPC (see decision of the Enlarged Board of Appeal G 1/03; OJ EPO 2004, page 413, point 2.5.2).

9. The general part of the description of the patent contains two references to this feature, namely in paragraphs [0029] and [0033]. A further reference to the harvesting of *L. intracellularis* in suspension cultures which is "*preferably done when 50-100% of the cells are infected*" can be found in paragraph [0028]. None of these references mentions any limitation to the type and nature of the cultured cells. This is also in line with the disclosure in paragraph [0016], where it is stated that "*numerous cell lines can be used*", although "*the preferred culture cells are HEp-2, McCoys or IEC-cells*".

10. Examples 2 and 3, which are concerned with the growth of *L. intracellularis* in suspension cultures of HEp-2 cells and of McCoy cells, do not give any information with regard to the specific level of infection. Such information is also not disclosed in Examples 4 and 5, both describing cultures in suspension of HEp-2 cells (cf. paragraphs [0070]-[0071] and [0094]-[0095]). Only Example 6 mentions that an infection rate of "*approximately 100%*" is observed in *L. intracellularis* grown in a suspension of McCoy cells (cf. paragraph [0114]). Thus, the Examples of the patent do not support the drawing of a definite conclusion with

regard to the achievement of the claimed infection rate in culture suspensions of cells other than McCoy cells.

11. This is confirmed by the experimental evidence provided in documents D91/91a and D97, which report that an infection rate of 100% at day 7 p.i. is achieved by using McCoy cells in suspension. However, this evidence also shows that the infection rate at day 7 p.i. is only 50% when IEC-18 cells, another preferred cell type according to the patent, are used in suspension (cf. Table 1 of D91/D91a and Figure 1 of D97). Although this infection rate is high when compared with the infection achieved with IEC-18 cells grown in monolayer culture (2.9% infection at day 7 p.i.; Figure 1 of document D97), it is far away from the required "*greater than about 70%*".

12. Document D97 discloses that "*the fact that the IEC-18 suspension culture was rising steadily to an infection rate of 50% at day 7* ***does not exclude*** *that a higher rate of 70% or more would have been reached upon a slightly longer cultivation. This* ***suggests*** *that the actual immortalised cell type ... is, unexpectedly, not a crucial factor to this highly raised infectivity rate*" (emphasis added by the board) (cf. page 3, point 8 of document D97). These speculations are a far cry from certain and convincing evidence demonstrating that the infection rate required by claim 1 is actually achieved with IEC-18 cells in suspension. Rather, the data provided in this experimental evidence casts serious doubt upon whether such an infection rate can be achieved with other preferred cells disclosed in the patent, or with any other types of non-preferred host cells.

13. In fact, as shown in Figure 2 of document D5, the percentage of infected IEC-18 cells grown in monolayer cultures also rises steadily to a maximum value of 20% at day 7 p.i. However, it remains stable at this value until day 9 p.i. and declines thereafter to a significantly lower value. There is thus no reason to expect that the infection rate of IEC-18 cells in suspension will necessarily continue to rise after day 7 p.i. It is not derivable in a convincing manner from the experimental evidence disclosed in documents D91/ D91a and D97 that an infection rate greater than about 70% can actually be achieved with IEC-18 cells in suspension. Indeed, prior art on file (*inter alia* document D3), although dealing with monolayer cell cultures, provides evidence that, for *L. intracellularis* and for other obligate intracellular bacteria (such as *Chlamydia*), both the degree of infection and the number of heavily infected cells depend to a great extent on the specific type and nature of the infected host cell (epithelial/non-epithelial cells, fast-growing/slow-growing, etc.).

14. The board, in view of the evidence on file, reaches the conclusion that the high infection rate required by claim 1 has been clearly and convincingly shown for McCoy cells in suspension only. Serious doubts substantiated by verifiable facts, exist as to whether such a high infection rate can be achieved when other types of host cells, including the preferred IEC-18 rat intestinal epithelial cells (cf. paragraph [0016] of the patent), are used.

15. Thus, the Main Request and Auxiliary Requests I and III do not fulfil the requirements of Article 83 EPC.

Auxiliary Request II

Article 100(b) EPC; Article 83 EPC
Claim 13

16. Claim 13 of Auxiliary Request II is directed to "*a method for producing an* ***attenuated*** *L. intracellularis strain*" (emphasis added by the board) (cf. point XI *supra*). Claims 1 and 12 of the Main Request and Auxiliary Requests I to V underlying the decision T 1846/10 were both directed to "*a method for producing a live* ***vaccine*** *against L. intracellularis*" (emphasis added by the board) (cf. T 1846/10, *supra*, items IV, VI and point 47 of the Reasons).

17. In the statement setting out the Grounds of Appeal and in respondent's reply thereto, both parties consistently stated that they regarded the subject-matter of claim 13 of Auxiliary Request II to be a method for producing an attenuated *L. intracellularis* strain "*suitable as a live vaccine*", i.e. having all properties of a vaccine. In its communication pursuant to Article 15(1) RPBA, the board informed the parties that the subject-matter of the claim could also be interpreted broadly, namely to refer to a method merely achieving a reduction of the pathogenicity of *L. intracellularis*. The board drew the parties' attention to decision T 1846/10 and stated that, if the term "*attenuated*" was interpreted narrowly and thus equated to "*suitable as a live vaccine*", it was likely to come to the same conclusion as that reached in T 1846/10, namely that the patent does not disclose this subject-matter in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art (cf. T 1846/10, *supra*, points 4-46 of the Reasons).

18. Whilst the appellant did not reply to the board's communication, the respondent filed further submissions

in reply thereto, wherein it argued that the correct interpretation of claim 13 of Auxiliary Request II required that the product of the claimed method, an "*attenuated*" strain, had to be seen as being "*suitable as a live vaccine*", in line with the *"narrow"* interpretation of this term. At the oral proceedings, the respondent confirmed this interpretation of the subject-matter of claim 13. Based on this interpretation, the respondent gave a detailed analysis of the reasoning of decision T 1846/10, in order to convince the board that a wrong decision had been taken. The respondent argued that the decision taken on this subject-matter by the board in decision T 1846/10 with regard to the requirements of Article 83 EPC, cannot be subject to the doctrine of *res judicata* for the present case since the wording of the claims is different as are the facts and evidence on file. Hence the respondent concludes that the board in the present case is not obliged to, and should not, find that claim 13 of Auxiliary Request II does not meet the requirements of Article 83 EPC (cf. point XV *supra*).

19. Taking account the arguments put forward by both parties in the written procedure and at the oral proceedings, the board sees no reason not to apply the "*narrow*" interpretation to construe the subject-matter of claim 13, which consequently, although not having exactly the same wording, is identical to the subject-matter of claim 12 of the Main Request in decision T 1846/10.

20. The application underlying the patent in the present case is the parent of the divisional application underlying T 1846/10. The appellant and respondent in the present case were also the appellant and respondent respectively in T 1846/10.

21. In T 1846/10, the board found that claim 12 of the Main Request before it did not meet the requirements of Article 83 EPC.

22. Independent claim 12 of the Main Request in T 1846/10 read as follows:

> "12. A method for producing a live vaccine against *L. intracellularis*, wherein said vaccine comprises an attenuated *L. intracellularis* strain, comprising the steps:
> (1) producing an attenuated *L. intracellularis* strain comprising obtaining culture cells infected with *L. intracellularis* bacteria, incubating said infected cells at an oxygen concentration of 0 percent to about 18 percent, agitating said infected cells so as to cultivate said bacteria while maintaining said infected cells in suspension, passaging at least a portion of said cultivated bacteria, harvesting at least a portion of said cultivated bacteria, and selecting for an attenuated strain to provide an attenuated *L. intracellularis* bacteria; and
> (2) admixing said attenuated *L. intracellularis* in an acceptable pharmaceutical carrier."

23. Claim 13 of Auxiliary Request II in the present case reads as follows:

> "13. A method for producing an attenuated L. intracellularis strain comprising obtaining culture cells infected with L. intracellularis bacteria, incubating said infected cells at an oxygen concentration of 0 percent to about 18 precent, agitating said infected cells so as to cultivate

said bacteria while maintaining said infected cells in suspension, passaging at least a portion of said cultivated bacteria, harvesting at least a portion of said cultivated bacteria, and selecting for an attenuated strain to provide an attenuated L. intracellularis bacteria." (cf. points XI-XII *supra*).

24. The wording of claim 12 of the Main Request in case T 1846/10 is not identical to the wording of claim 13 of Auxiliary Request II in the present case. Nevertheless the board has concluded that the subject matter of these claims is the same; see points 16 to 19 above.

25. The question therefore arises whether the application of the doctrine of *res judicata* is appropriate in this case. If it is, the board would find that claim 13 of Auxiliary Request II did not meet the requirements of Article 83 EPC.

26. The Boards of Appeal have an established practice of applying the *res judicata* doctrine; see T 51/08 of 7 May 2009, points 1 to 4 of the Reasons. The *res judicata* doctrine undoubtedly falls under those "principles of procedural law generally recognised in the Contracting States", referred to in Article 125 EPC.

27. For *res judicata* to apply, the same question has to have been decided in both T 1846/10 (*supra*) and the present case. The "*same question*" requirement is not to be applied in a mechanical, formalistic way so as to require that the claims under consideration in the cases have to be identical. Rather the boards examine whether the subject matter of the claims is the same (see T 790/10 of 18 December 2012; T 1155/13 of 7 May

2014, point 6.2 of the Reasons). The board has already decided affirmatively upon this point. The compliance of these claims with Article 83 EPC was the issue in T 1846/10 and is the issue in the present case.

28. As regards the facts and evidence on file, the board considers that the essential facts in the present case are the experimental data and the results disclosed in Examples 5 and 6 of the patent; both examples concern the efficacy of a vaccine produced by the method of claim 13 in hamster and swine, respectively. Except for the declaration of Dr. S. McOrist (document D67 in T 1846/10), all other declarations, experiments, prior art and one post-published patent application explicitly referred to in decision T 1846/10 (cf. T 1846/10, *supra*, point III of the Facts and Submissions; documents D1, D48, D50, D55 and D64 in that decision correspond to documents D4, D91/D91a, D89, D98 and D90 in the present appeal proceedings) have also been filed in the present appeal proceedings. The board notes that although the declaration of Dr. B. Eichenmüller, D64 in T 1846/10 and D90 in the present appeal, are not identical, they have essentially the same content. There are only three other documents cited in decision T 1846/10 (post-published scientific publications D65, D66 and D68). These documents were mentioned in the context of Example 6 of the patent and were considered not relevant by the board in decision T 1846/10 (cf. T 1846/10, *supra*, points 30 and 41 of the Reasons).

29. In addition to the reasoning put forward by the respondent at oral proceedings before the board (cf. point 18 *supra*), a further decisive factor for the board to be convinced that the facts and evidence in the present case are the same as in the case underlying

decision T 1846/10, are the respondent's submissions filed in reply to the board's communication pursuant to Article 15(1) RPBA (cf. point VIII *supra*). These submissions are a straightforward review of the conclusion arrived at by the board in decision T 1846/10, wherein reference is also made to the preliminary, non-binding opinion of the board in that case expressed in the communication pursuant to Article 15(1) RPBA (Exhibit 1) and to the respondent's reply thereto (Exhibit 2).

30. At oral proceedings before the board the respondent referred to a further declaration of a technical expert. This declaration was neither filed in reply to the Grounds of Appeal nor in reply to the board's communication. Under the particular circumstances of the present case, the board drew the respondent's attention to the possible non-admissibility of such a declaration if filed at the latest stage of the appeal proceedings. The respondent did not file this declaration and thus, it is not part of the evidence on file.

31. Thus, the board concludes that the doctrine of *res judicata* is applicable to this case, and that applying the doctrine, claim 13 of Auxiliary Request II does not meet the requirements of Article 83 EPC.

Auxiliary Request IV
Article 100(b) EPC; Article 83 EPC
Claims 1-12

32. Claims 1-12 of this auxiliary request are directed to methods for cultivating *L. intracellularis* bacteria in suspension culture wherein the infected host cells are defined as being McCoy cells. Claims relating to a

method for producing attenuated *L. intracellularis* strains have been deleted from this request (cf. point XII *supra*). Thus, none of the objections raised under Article 83 EPC against the Main Request and Auxiliary Requests I-III above applies to this request.

33. Former opponent 01, by referring to experimental data filed with its Grounds of Appeal, has objected that *L. intracellularis* bacteria cannot be cultivated in free suspensions of McCoy cells, i.e. in suspensions without microcarriers, beads, etc. (cf. point XIV *supra*). According to the patent, the use of microcarriers, beads, etc. for this type of adherent (anchorage-dependent) cells, is a preferred embodiment of the invention, but is not essential for carrying out the claimed method (cf. paragraph [0031] of the patent). Indeed, whilst in Example 3 of the patent microcarriers/beads are said to be used (cf. paragraphs [0059]-[0061]), there is no reference to such material in Example 6 (cf. paragraph [0114]).

34. The patent does not give detailed information on the specific conditions of the suspension culture used in Example 6. Such information is, however, provided in the experimental evidence disclosed in documents D91/ D91a and D97, wherein McCoy cells are cultured in free suspensions without microcarriers or beads. It is important to note that different appearance, cell density and infection were obtained in these experiments for the two types of adherent cells used (IEC-18 and McCoy). It is stated that the McCoy cells are "*forming clusters of cells*" resulting in "*significant clumping issues*" (cf. page 1, last paragraph and page 2, second paragraph of documents D91/D91a). Thus, the probative value of the

experimental data filed with opponent 01's Grounds of Appeal is at least questionable.

35. Indeed, during the course of the first appeal procedure in which this experimental data was late filed (cf. T 692/08, *supra*), the respondent questioned the validity of this data and its admissibility. No decision was taken on this issue by the board in the first appeal procedure or by the opposition division after the remittal. The status of this experimental data is not clearly established in the present, second appeal procedure. It is not contained in the consolidated list of documents annexed to the Minutes of the oral proceedings before the opposition division leading to the decision under appeal. However, in view of the questionable probative value of this data (cf. point 34 *supra*), it is not necessary for the board to enter into further detail on this issue.

36. Thus, Auxiliary Request IV fulfils the requirements of Article 83 EPC.

Article 100(a) EPC; Article 56 EPC
Claims 1-10 and 12

37. The closest prior art document D5 discloses a method for cultivating *L. intracellularis* bacteria in a monolayer culture of rat enterocyte IEC-18 cells infected with *L. intracellularis*. The infected cells are incubated at a reduced oxygen concentration of less than 18%, and harvested when most of the cells are infected and when many heavily infected cells (HIC) are present (between days 5 and 7 p.i.). Whilst the level of infection of the IEC-18 cells exposed directly to the bacteria is reported to be between 6.29 (at 5 days p.i.) and 2.90 (at 7 days p.i.), the percentage of

infected cells arrives at about 20% when the IEC-18 cells are exposed to supernatant fluid from IEC-18 cells infected directly with *L. intracellularis* bacteria (cf. Table 1 and Figure 2 of document D5). Document D5 acknowledges that "[t]*he cell culture system described has many deficiencies, not the least of which is the apparent failure of many bacteria to established cell infection once associated with cells*" (cf. page 1142, left-hand column, third paragraph from the bottom).

38. Starting from the disclosure in this document, the objective technical problem to be solved is the provision of an improved method for cultivating *L. intracelluaris* bacteria. The subject-matter of claim 1, over its entire scope, provides a solution to this problem, as shown by the patent itself and by the evidence on file (cf. points 9-14 and 33-35 *supra*).

39. A person skilled in the art of culturing bacteria was well aware of the limitations of monolayer cell cultures and knew the advantages provided by suspension cultures, in particular by the microcarrier bead culture technology, that had already been used for growing the obligate intracellular bacterial parasite *Chlamydia trachomatis* in McCoy cells (cf. *inter alia*, document D6). Thus, it remains to be answered whether it would have been obvious for him/her to amend the teaching in the closest prior art and to apply this technology to *L. intracellularis* with a reasonable expectation of success.

40. According to prior art on file (cf. *inter alia*, document D3), obligate intracellular bacteria are a phylogenetically diverse group of bacteria with different life cycles based on their specific

biochemical and molecular properties. The interaction of these bacteria with their host cells involves a complex sequence of events, such as membrane attachment and invasion of the host cell (coated pits, vesicles, receptor mediated, etc.), replication inside these cells (either within vacuoles or free in the cytoplasm), and eventually leaving the host cell (cf. *inter alia*, page 255, paragraph bridging left and right-hand column, page 258, right-hand column, third paragraph to page 259, left-hand column, last paragraph of document D3). The characteristics and properties of all these events depend on the specific obligate intracellular bacteria and their specific host cells. Thus, for *in vitro* growth of obligate intracellular bacteria, conditions have often been developed to resemble the natural *in vivo* habit. Indeed, most, if not all, *in vitro* growth studies of *L. intracellularis* have been carried out by using monolayers of intestinal cells, i.e. the natural environment of these bacteria, the rat enterocyte IEC-18 cell line being the most preferred host cell (cf. *inter alia*, documents D3 to D5).

41. Moreover, while some of these obligate intracellular bacteria, such as *Chlamydia*, are known to have a very broad range of permissive host cells, other obligate intracellular bacteria, such as *L. intracellularis*, are much more restrictive. Prior art on file shows that differences in the obtained number of cells infected and heavily infected with *L. intracellularis* are even present between different intestinal host cells (cf. *inter alia*, document D3).

42. In view of the fact that fibroblast McCoy cells as host cells in suspension are far away from the natural *in vivo* habitat of this bacterium, it seems to be highly

doubtful that a skilled person would have applied the teaching of document D6 in a straightforward manner for cultivating *L. intracellularis*. Moreover, the skilled person could not have any expectation to succeed in obtaining a high number of infected cells, which in fact is much higher than the level of infection achieved under conditions resembling the natural environment of this bacterium (cf. documents D5, D91/ D91a and D97). Thus, the board is convinced that the selection of McCoy cells as host cells in suspension was not obvious for a skilled person and that the achievement of such high level of infection could not have been reasonably expected.

43. Therefore, the subject-matter of claims 1-10 and 12 fulfils the requirements of Article 56 EPC.

Claim 11

44. The closest prior art document D4 discloses the culturing of *L. intracellularis* bacteria in monolayers of rat enterocytes IEC-18 host cells and the further passaging of the bacteria in IEC-18 cells. The bacteria are then used for pig infection, demonstrating thereby that *L. intracellularis* reproduces and is thus the cause of proliferative enteropathy in pigs. The number of passages of bacteria grown in cells and used to infect each pig varies from as low as only 3 passages to as high as 21 passages (cf. page 4287, Table 1). Although it is disputed among the parties whether document D4 discloses attenuated *L. intracellularis* (see also, in this context, T 1846/10, *supra*, point 7 of the Reasons), the document explicitly states that "[t]*he doses used were considered to be relatively small but were similar for groups receiving each passage, indicating that differences in lesions*

produced may be due to a diminution in pathogenecity of an isolate passaged multiply in vitro" (cf. page 4291, left-hand column, last full paragraph from the bottom).

45. Starting from this prior art, the objective technical problem is the provision of alternative *L. intracellularis* strains with improved (attenuated) properties.

46. In Example 6 of the patent, the ATCC 55783 strain is described as the result of growing *L. intracellularis* continuously in a culture of McCoy cells in suspension for 29 weeks and passaged for additional 11 weeks, i.e. a total of 40 weeks (cf. paragraph [0114] of the patent). Based on the experimental data disclosed in documents D91/D91a which show that under these conditions 100% infection is achieved at 7 days p.i., the deposited strain has most likely been passaged 40 times, i.e. about twice as often as the highest number of passages reported in document D4 (see, in this context, T 1846/10, *supra*, points 39-40 of the Reasons). The respondent has referred to the advantageous properties of this strain and its use as master seed of a commercial vaccine. Indeed, the advantageous properties of this strain have already been acknowledged in decision T 1846/10, wherein the board allowed a claim directed to a method for producing a live vaccine against *L. intracellularis* based on the attenuated *L. intracellularis* bacteria deposited as ATCC 55783 (cf. T 1846/10, *supra*, point VII of the Facts and Summary and points 48-59 of the Reasons). Thus, the *L. intracellularis* strain deposited as ATCC 55783 solves the objective problem formulated above. Moreover, due to the unpredictability of the attenuation process (cf. T 1846/10, *supra*, point 7 of the Reasons), the achievement of the *L. intracellularis*

strain deposited as ATCC 55783 was not obvious to a skilled person. The person skilled in the art had no particular reason to expect success that such a strain could indeed be produced (cf. T 1846/10, *supra*, points 57-58 of the Reasons).

47. Thus, the subject-matter of claim 11 meets the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the department of first instance with the order to maintain the patent with the following claims and a description to be adapted thereto:

Claims 1 to 12 of Auxiliary Request IV filed under cover of a letter dated 14 July 2016.

The Registrar: The Chairman:

A. Wolinski M. Wieser

Decision electronically authenticated