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**Datasheet for the decision  
of 7 May 2019**

**Case Number:** T 1894/15 - 3.3.10

**Application Number:** 06760544.4

**Publication Number:** 1890996

**IPC:** C07C237/26, C07C231/24

**Language of the proceedings:** EN

**Title of invention:**

CRYSTALLINE SOLID FORMS OF TIGECYCLINE AND METHODS OF PREPARING  
SAME

**Patent Proprietor:**

Wyeth LLC

**Opponents:**

Taylor Wessing LLP  
Galenicum Health S.L.

**Headword:**

**Relevant legal provisions:**

EPC Art. 100(a), 56

**Keyword:**

Inventive step - (no)

**Decisions cited:**

T 1422/12

**Catchword:**



**Beschwerdekammern**

**Boards of Appeal**

**Chambres de recours**

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Case Number: T 1894/15 - 3.3.10

**D E C I S I O N**  
**of Technical Board of Appeal 3.3.10**  
**of 7 May 2019**

**Appellant:** Wyeth LLC  
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**Representative:** Galenicum Health S.L.  
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**Party as of right:** Taylor Wessing LLP  
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**Decision under appeal:** **Interlocutory decision of the Opposition**  
**Division of the European Patent Office posted on**  
**30 July 2015 concerning maintenance of the**  
**European Patent No. 1890996 in amended form.**

**Composition of the Board:**

**Chairman**            P. Gryczka  
**Members:**           R. Pérez Carlón  
                            F. Blumer

## Summary of Facts and Submissions

- I. The patent proprietor and opponent 2 appealed the decision of the opposition division concerning the maintenance of European patent No. 1 890 996 in the form of the auxiliary request then pending.

These parties are referred to in the following as the appellant-opponent and the appellant-patent proprietor.

- II. Two notices of opposition had been filed on the grounds of added subject-matter (Article 100(c) EPC), insufficiency of disclosure (Article 100(b) EPC), and lack of novelty and inventive step (Article 100(a) EPC).

- III. The party as of right (opponent 1) made no substantive submission during these appeal proceedings.

- IV. The documents filed during the opposition and appeal proceedings include the following:

D1: US 5,675,030

D9: Submission of the appellant-patent proprietor during examination proceedings dated 13 December 2011

D10: Byrn *et al.* "Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations" (Review), *Pharmaceutical Research*, Vol. 12, No. 7, 1995, pages 945-954

D12: Nelson, "The chemistry and cellular biology of the tetracyclines", *Tetracyclines in Biology, Chemistry and Medicine*, Nelson, Hillen and Greenwald (ed.), 2001 Birkhäuser Verlag/ Switzerland, pages 3-6 and 16-24

- D21: Burger, Ratz, "The Polymorphic Drug Substances of the European Pharmacopoeia, Part 6: Physical and Chemical Stability of Amorphous and Crystalline Tetracycline Hydrochloride", Scientia Pharmaceutica, 58, 69-75 (1990)
- D24: Declaration of Dr. Ivan Marziano dated 19 April 2016

V. On the issue of inventive step, the opposition division concluded that example 8 of document D1 was the closest prior art, and that it disclosed amorphous tigecycline. The problem underlying the claimed invention was to provide tigecycline in a form more stable with respect to epimerisation. The problem was solved by the solid form of claim 1. As there was no suggestion in the prior art that chemical stability in terms of epimerisation could be improved by a crystalline form of tigecycline, the claimed solution was inventive.

VI. Claim 1 of the patent as granted, which is the appellant-patent proprietor's main request, reads as follows:

*"Form I tigecycline having X-ray powder diffraction peaks at  $5.2 \pm 0.2$  °2 $\theta$ ,  $11.1 \pm 0.2$  °2 $\theta$ ,  $8.3 \pm 0.2$  °2 $\theta$ , and  $24.8 \pm 0.2$  °2 $\theta$ ."*

VII. Claim 1 of the auxiliary request, which is the request considered allowable by the opposition division, reads as follows:

*"Form I tigecycline having X-ray powder diffraction peaks at 5.2, 8.3, 10.4, 11.1, 13.2, 13.7, 14.7, 15.6, 16.6, 19.0, 19.3, 19.9, 21.2, 22.4, 23.1 and  $24.8 \pm 0.2$  °2 $\theta$ ."*

VIII. The arguments of the appellant-patent proprietor, where relevant for the present decision, were as follows:

Example 8 of D1 disclosed amorphous tigecycline and was the closest prior art. The problem underlying the claimed invention was to provide a solid form of tigecycline more stable towards epimerisation. The solution, namely Form I, was not obvious having regard to the prior art, as neither D1 nor D12 related to solid forms and D21 concerned a hydrochloride of another tetracycline and would not have prompted the skilled person towards the claimed solution. For these reasons, the subject-matter of the main request and the auxiliary request was inventive.

The appellant-patent proprietor acknowledged that the arguments would not differ regardless of which of the two requests on file were considered.

IX. The arguments of the appellant-opponent, where relevant for the present decision, were as follows:

If it were to be considered that example 8 of D1 disclosed amorphous tigecycline, the appellant-opponent agreed with the appellant-patent proprietor on the definition of the problem underlying the claimed invention and considered that the claimed solid form credibly solved that problem. However, it argued that the claimed solution was obvious as tetracyclines were known to be prone to epimerisation. It was further known that water induced this reaction and that crystalline tetracycline was less hygroscopic than the corresponding amorphous form. The solid form of claim 1 of the main request and of the auxiliary request was thus not inventive.

- X. Oral proceedings before the board of appeal took place on 7 May 2019.
- XI. The final requests of the parties were as follows:
- The appellant-patent proprietor requested that the decision under appeal be set aside and that the patent be maintained as granted or, in the alternative, that the appeal of the appellant-opponent be dismissed, i.e. that the patent be maintained on the basis of the auxiliary request as maintained by the opposition division.
  - The appellant-opponent requested that the decision under appeal be set aside and that European patent No. 1 890 996 be revoked.
- XII. At the end of the oral proceedings, the decision was announced.

### **Reasons for the Decision**

1. The appeal is admissible.
2. As the board found that the subject-matter of none of the requests relates to inventive subject-matter, it is not necessary to decide on any other point.
3. Closest prior art

The parties considered, in agreement with the opposition division, that if the solid form of tigecycline of claim 1 of any of the requests on file were novel, the solid form disclosed in example 8 of



document D1 would be the closest prior art.

However, the parties were divided as to the structure of that solid form. The appellant-patent proprietor considered, in accordance to its experimental evidence D24 and to the conclusion of the opposition division, that example 8 of D1 disclosed amorphous tigecycline. The appellant-opponent argued that example 8 disclosed a crystalline form of it.

The question of which solid form of tigecycline is disclosed by example 8 of D1 can, however, be left aside. This is because the board holds that even if example 8 disclosed amorphous tigecycline, in accordance to the appellant-patent proprietor's position and the opposition division's conclusion, the claimed subject-matter would nevertheless have been obvious for the reasons explained below.

4. Technical problem underlying the invention

According to the appellant-patent proprietor, the technical problem underlying the claimed invention is the provision of a solid form of tigecycline with improved stability towards epimerisation in comparison with amorphous tigecycline.

5. Solution

The solution to this technical problem is the claimed solid form of tigecycline, characterised by its X-ray powder diffraction peaks.

6. Success

It was not in dispute that the claimed form of

tigecycline credibly solves the problem as formulated in point 4. above.

Having regard to the data provided by the appellant-patent proprietor in the letter dated 13 December 2011 (D9, table on page 2), the board has no reason to conclude otherwise.

7. It thus remains to be decided whether the proposed solution to the objective problem defined above would have been obvious from the prior art.
- 7.1 The patent in suit acknowledges that it was known at the filing date that tigecycline tended to degrade and for this reason its powders were prepared and processed under low-oxygen and low-temperature conditions [0003].
- 7.2 At the filing date, epimerisation was known to occur with tetracyclines in general (D12, page 23; D1, column 1, lines 27-28) and of substituted N-glycylamido tetracyclines (D1, column 2, last paragraph), such as tigecycline (compound 5f of D1), in particular. This was not in dispute.
- 7.3 The appellant-patent proprietor argued that there was no indication in the prior art that a crystalline form of tigecycline would epimerise less than the corresponding amorphous form.
- 7.4 However, it would have been obvious to the skilled person that the claimed crystalline solid form of tigecycline would show less epimerisation.

Tigecycline belongs to the general class of tetracycline antibiotics. These compounds have four condensed six-membered rings, usually named A to D

(D12, page 19, Figure 10). Epimerisation takes place in position 4 of ring A (D12, page 23).

D1 and D12 disclose that the presence of water induces epimerisation (D12, page 23, line 16; D1, column 2, line 62).

Document D21 relates to tetracycline and discloses that "the amorphous phase is produced, which as far as light and moisture is concerned, is chemically much less stable than the crystalline form" (abstract, lines 6-7). In point 3 (discussion), D21 discloses that varying properties of tetracycline were due to varying content of the amorphous phase in a solid form. Tetracycline hydrochloride exhibiting high crystallinity was found not to be hygroscopic and to be chemically rather stable (page 73, lines 12-13).

This finding is in agreement with the general knowledge in the art with respect to solid forms, as reflected by D10, that amorphous forms are in general more soluble, take up more water and are sometimes less chemically stable than the corresponding crystalline form (page 952, right column, lines 12-16).

Thus, the skilled person, would have known that:

- Water enhances epimerisation of tetracyclines (D12), including tigecycline (D1).
- Crystalline forms of tetracycline are known to be less hygroscopic and chemically more stable than the corresponding amorphous solid (D21).

Having regard to this information and trying to reduce the epimerisation of amorphous tigecycline, the skilled

person would have tried to crystallise tigecycline, with the expectation of solving that problem. Form I is only one among equally suitable crystalline compounds which solve this problem. For these reasons, the form of tigecycline of claim 1 of the main request and the auxiliary request is not inventive within the meaning of Article 56 EPC.

- 7.5 In the context of claim 1 of the auxiliary request, the opposition division concluded that neither D12 nor D21 related to tigecycline antibiotics but to tetracyclines, and that the teaching of these documents did not apply to tigecycline.

However, tigecycline (D1, column 7, compound 5f) is a tetracycline antibiotic having the four-ring core structure of tetracycline (D12, Figure 17 on page 23, compound I). The reactive part of the molecule (ring A as defined in D12, page 19) is identical. The difference between these compounds is merely the substitution of the aromatic ring (ring D), which is not part of the conjugated system bearing the epimerisable C4 moiety of ring A, and which the skilled person would not have expected to have any bearing in the reactivity of the latter.

- 7.6 The appellant-patent proprietor argued that D1 put forward a different solution to the technical problem of epimerisation. The board can only answer that, if D1 disclosed the claimed solution, the present argument would have been under the heading of novelty.

- 7.7 The appellant-patent proprietor also argued that document D21 related to tetracycline hydrochloride and not to its free base and that D21 did not deal with the problem of epimerisation.

However, D21 relates to tetracycline chemical stability, which includes epimerisation. It mentions epimerisation in the introduction, in the context of "aqueous solutions and dosage forms". Even the appellant-patent proprietor acknowledged in its written submissions that epimerisation "has plagued the tetracycline class of antibiotics for many years, indeed decades" (response of the appellant-patent proprietor dated 19 April 2016, point 3.4.1; letter dated 6 December 2018, page 2, first full paragraph). The skilled reader would thus have known that, in the context of tetracyclines, "chemical stability" embraces epimerisation. Be that as it may, the board sees in D21 a teaching for the skilled person on how to reduce moisture absorption of a tetracycline solid phase, which is known to be directly linked to epimerisation (D12, D1).

The skilled person would have considered any information on the stability of solid tetracyclines in the context of the claimed problem, regardless of whether the tetracyclines are in the form of a free base or as a chlorhydrate. In fact D21 merely proves that the general behaviour of amorphous vs. crystalline forms in terms of stability and hygroscopicity (D10) holds true for tetracyclines.

These arguments are thus not convincing.

- 7.8 The appellant-patent proprietor argued that the substituents in ring D of tigecycline, which tetracycline lacks, would influence the crystallisation of the former.

The board can only agree with this argument. The

skilled person would not have known *a priori* whether it would be possible to crystallise tigecycline. However, tigecycline is a solid compound, and the issue here is whether, in trying to diminish epimerisation, the skilled person would have considered a crystalline form to be a solution to that problem. For the reasons given above, it is considered that they would have.

- 7.9 The appellant-patent proprietor also argued that it was difficult to understand how epimerisation could take place in the solid form as it involved an initial protonation.

However, D12 and D1 disclose that the mere presence of water induces epimerisation. Epimerisation in the solid form is considered to be linked to hygroscopicity. Thus, this argument is also not convincing.

- 7.10 Lastly, the appellant-patent proprietor argued that, in T 1422/12, the present board concluded that a different crystalline form of tigecycline was inventive over that of example 8 of D1, which was considered to be amorphous tetracycline. As the facts of the case were the same, it argued that the board should decide along the same lines in the present case.

However, neither D12 nor D21 were available to the board in T 1422/12. The facts of the case are thus different, and the conclusion does not necessarily have to be the same.

## Conclusion

8. The ground of opposition defined in Article 100(a) EPC precludes the maintenance of the patent as granted, and the auxiliary request is not allowable.

**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:



C. Rodríguez Rodríguez

P. Gryczka

Decision electronically authenticated