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Datasheet for the decision of 17 January 2017

Case Number: T 0065/15 - 3.3.07

Application Number: 03744867.7

Publication Number: 1494646

IPC: A61K9/00

Language of the proceedings: EN

Title of invention:
INTRAVAGINAL MATRIX DRUG DELIVERY DEVICES

Patent Proprietor:
Warner Chilcott (Ireland) Limited

Opponents:
Bayer Pharma Aktiengesellschaft /
Bayer Intellectual Property GmbH

Relevant legal provisions:
EPC Art. 100(b), 54(2), 56, 84

Keyword:
Sufficiency of disclosure - main request (yes)
Novelty - main request (yes)
Inventive step - main request (yes)
Claims - clarity in opposition proceedings

Decisions cited:
G 0003/14

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Case Number: T 0065/15 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 17 January 2017

Appellants: (Opponents)	Bayer Pharma Aktiengesellschaft / Bayer Intellectual Property GmbH Müllerstrasse 178/Alfred-Nobel-Strasse 10 13353 Berlin/40789Monheim (DE)
Representative:	Hartmann, Uwe Bayer Intellectual Property GmbH Creative Campus Monheim Alfred-Nobel-Straße 10 DE-40789 Monheim (DE)
Respondent: (Patent Proprietor)	Warner Chilcott (Ireland) Limited Building B Xerox Technology Park Dundalk Louth (IE)
Representative:	Kelly, Donal Morgan FRKelly 27 Clyde Road Dublin D04 F838 (IE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 10 November 2014 concerning maintenance of European patent No. 1494646 in amended form.**

Composition of the Board:

Chairman	I. Beckedorf
Members:	A. Usuelli
	D. Boulois

Summary of Facts and Submissions

I. European patent No. 1 494 646, based on European patent application No. 03744867.7, was opposed on the grounds that its subject-matter lacked novelty and inventive step, was not sufficiently disclosed and extended beyond the content of the application as filed.

The following documents were among those cited during the first-instance proceedings:

D1: WO 02/076426
D2: US 4,155,991

II. By an interlocutory decision posted on 10 November 2014, the opposition division maintained the patent in amended form. The decision was based on a main request filed during the oral proceedings held on 18 September 2014.

Claim 1 of this request read as follows:

"1. A method for altering the release characteristics of an intravaginal matrix drug delivery device, the method comprising preparing the drug delivery device by a process comprising the steps of:
(i) combining less than 30% (w/w) of at least one therapeutic agent with at least one biocompatible elastomeric polymer, and in which the at least one biocompatible elastomeric polymer is silicone and the at least one therapeutic agent has a solubility in silicone oil at 25°C of less than 0.1 mg/ml, to form a mix for preparing a drug delivery device having increased day 1 release rates;
(ii) curing said mix to form a polymer matrix, in which the biocompatible elastomeric polymer is silicone and

either the curing step is carried out at 50-100°C for 1-10 minutes, optionally for 1.5 to 5 minutes, or the curing step is carried out at 15-25°C for 1-24 hours; and
(iii) maturing said shape-retaining polymer matrix under temperature and time conditions sufficient to form the intravaginal drug delivery device, in which said maturing step is carried out at 40-100°C for 2-72 hours".

III. In its decision, the opposition division held that the subject-matter of the main request complied with the requirements of Article 123(2) and 123(3) EPC and that it was sufficiently disclosed.

The post-published document D1 was a prior-art document pursuant to Article 54(2) EPC in that the subject-matter of the main request did not benefit from the claimed priority date.

Document D1 did not disclose any device prepared in a process comprising a maturing step according to step (iii) of claim 1 and containing less than 30% of a therapeutic agent. The subject-matter of the main request was therefore novel over D1. Furthermore, the main request was also novel in view of document D2, since several selections within the general disclosure of this document were necessary in order to arrive at a device as defined in claim 1.

As to inventive step, the opposition division considered that D1 was the closest prior art. The device of claim 1 of the main request differed from the devices of D1 in that it was prepared by a process involving a maturing step. The technical effect due to this difference was an increase in the release rate of

the drug during the first day. This was demonstrated in example 5 of the patent. D1 disclosed in example 13 a device prepared by a process involving a maturing step, which differed from the device of claim 1 in that it contained an amount of drug above 30%. The experimental data disclosed in this example indicated a decrease in the day-1 release rate. Thus, the skilled person confronted with the the problem of increasing the day-1 release rate had no reason to perform a maturing step. Document D2 did not provide any teaching as to the effects of the vulcanisation steps on the drug release rate.

The subject-matter of the main request was therefore inventive.

IV. The opponents (hereinafter: the appellants) lodged an appeal against that decision in the prescribed form and within the prescribed time-limits. With the statement setting out the grounds of appeal they submitted the following document:

D11: Journal of Controlled Release 73 (2001), 121-136

V. In its reply to the appeal filed on 30 September 2015 the patent proprietor (hereinafter: the respondent) requested dismissal of the appeal, *i.e.* maintenance of the patent on the basis of the request deemed allowable by the opposition division, and filed two auxiliary requests.

VI. In a communication pursuant to Article 15(1) RPBA issued on 7 November 2016, the Board expressed the view that the main request complied with the requirement of sufficiency of disclosure and was novel over documents D1 and D2. Concerning the assessment of inventive step,

the Board indicated that document D1 was the closest prior art, in particular in view of the devices disclosed in examples 1 to 8 and 13.

VII. Oral proceedings were held on 17 January 2016, for the course of which reference is made to the minutes.

VIII. The appellants' arguments in relation to the main request, as far as relevant to the present decision, may be summarised as follows:

(a) Sufficiency of disclosure

The claims of the main request also covered devices containing a combination of therapeutic agents. The patent however did not contain any data as to the drug release profile of these devices. The effect of increasing drug release on the first day was supported by a single example containing only acyclovir as active ingredient. It was doubtful whether this increased release was also present in devices containing a combination of active ingredients.

Dependent claims 6 to 8 related to embodiments wherein the method of claim 1 included an ageing step. Since this step could be carried out at a temperature ranging from 15-30°C, it was not clear how to stop it when the device was stored at room temperature.

(b) Novelty

Examples 1 to 8 of D1 disclosed a process for preparing intravaginal devices containing metronidazole in an amount of less than 30%. This active ingredient had low solubility in silicone oil, as confirmed in paragraph [0046] of the patent. The process involved a curing

step carried out at a temperature of 80°C for two minutes. Thus, the process of examples 1 to 8 had the same features as were defined in steps (i) and (ii) of claim 1 of the main request. Furthermore, example 13 of D1 described intravaginal rings which were prepared by a process comprising a post-curing step carried out at 60°C for 16 hours. This step was no different from the maturing step defined in point (iii) of claim 1 of the main request. The skilled person would have considered that the post-curing step of example 13 was also applicable to the devices of examples 1 to 8. Hence, D1 disclosed a process having all the features of claim 1 of the main request.

This claim was also anticipated by the disclosure of D2, which related to medicated vaginal rings. The feature requiring the amount of active ingredient to be less than 30% was disclosed in column 2, line 14. A vulcanisation step carried out for 1 to 6 hours at a temperature of 60°C to 120°C was disclosed in column 7, lines 3 to 4. Finally, metronidazole was disclosed as one of the possible active ingredients in column 8 of D2.

(c) Inventive step

Document D1 was the closest prior art for the assessment of inventive step. The process of claim 1 of the main request differed from the process of examples 1 to 8 of D1 in the requirement of including a maturing step. Example 5 of the patent showed a burst effect, *i.e.* an increased day-1 release of acyclovir, when the device was prepared by a process involving a maturing step. However, in this example the amount of active ingredient was less than 30%. The patent did not contain any data relating to devices containing

acyclovir as active ingredient in an amount above 30%. Thus, the patent did not provide any evidence as to the relevance of the amount of active ingredient. The technical problem was the provision of an alternative method for preparing intravaginal drug delivery devices. The devices of example 13 of D1 were prepared by a process comprising a post-curing step which was equivalent to the maturing step described in the patent in suit. Said maturing step had the purpose of improving the release characteristics of the intravaginal devices. Table 1 of D1 showed that the devices of examples 1 to 6 presented an enhanced day-1 release. In view of the teaching of example 13, the skilled person would have considered that this release could have been further increased by the addition of a maturing step. The advantages of carrying out a maturing step were also obvious in view of the teaching of document D11, which reported that during drying and storage steps there was a redistribution of the drug within the device. Accordingly, the subject-matter of claim 1 did not involve an inventive step. This conclusion also applied if the the formulation of the technical problem included an indication that the day-1 release was enhanced.

(d) Clarity

The subject-matter of claim 1 was defined as a result to be achieved and was therefore not clear. The absence of indications on how to interrupt the ageing step in claims 6 to 8 rendered these claims unclear. Claims 4 and 5 depended on claim 3. This dependency was inconsistent with the time ranges defined in these claims (12 to 30 hours in claim 3 vs 2 to 72 hours in claims 4 and 5). Thus, claims 3 and 4 likewise did not comply with Article 84 EPC.

IX. The respondent's arguments in relation to the main request, as far as relevant to the present decision, may be summarised as follows:

(a) Sufficiency of disclosure

Paragraph [0028] of the patent clearly described a method for preparing an intravaginal device containing less than 30% of active ingredient as required by claim 1. The skilled person had sufficient information to perform the invention over the whole area claimed. As to the ageing step, this could be interrupted by working at a temperature outside of the range 15°C to 30°C.

(b) Novelty

Documents D1 did not disclose the combination of all the features of claim 1 in a single disclosure. Hence, it did not anticipate the subject-matter of the main request. The same consideration applied in respect of D2. Moreover, the two-step curing process of D2 did not correspond to the curing step (ii) of claim 1 of the main request. Thus, document D2 did not anticipate claim 1 either.

(c) Inventive step

The closest starting point for the assessment of inventive step was represented by examples 1 to 8 of D1. The devices disclosed in these examples were prepared by a process which did not involve any maturing step as required by claim 1. Example 5 of the patent showed the effect due to this difference, namely an increase in the day-1 release. Example 13 of D1

showed that a post-curing step, equivalent to the maturing step of the patent in suit, had the effect of decreasing the day-1 release. Accordingly, the skilled person seeking to provide an intravaginal device with enhanced day-1 release had no reason to modify the process used in examples 1 to 8 by adding a post-curing step. D11 on page 124 described some phenomena causing the burst effect in intravaginal devices. However, this document did not provide any teaching on how to modify a device in order to obtain a burst effect. Moreover, the passage of page 124 of D11 related to hydrogel materials, while the devices of D1 were made from elastomers. Hence, the skilled person had no reason to combine D1 and D11. The subject-matter of the main request was therefore inventive.

X. The appellants requested that the decision under appeal be set aside and that the European patent No. 1 494 646 be revoked.

XI. The respondent requested that the appeal be dismissed (*i.e.* that the patent be maintained in amended form according to the main request found by the opposition division in the decision under appeal to meet the requirements of the EPC) or, in the alternative, that in setting aside the decision under appeal the patent be maintained in amended form on the basis of one of the sets of claims filed as first and second auxiliary requests with letter of 30 September 2015.

Reasons for the Decision

Main request

1. Sufficiency of disclosure

1.1 One of the appellants' arguments in relation to the requirement of sufficiency of disclosure is based on the observation that the claims of the main request also cover devices containing a combination of therapeutic agents. The patent however does not contain any data as to the drug release profile of these devices.

1.1.1 The Board notes that the patent describes in paragraph [0051] a general method for preparing an intravaginal matrix drug delivery device. Furthermore, example 5 shows that a device having the features of claim 1 and containing acyclovir as active ingredient presents the effect recited in claim 1, namely an increased day-1 release of the drug as compared with a device prepared in a process that does not comprise a maturing step.

The appellants' remark that the behaviour of a device containing a combination of drugs has not been investigated is correct. There are however no specific technical arguments or evidence brought forward by the appellants suggesting that the release profile of an agent having the concentration and solubility specified in claim 1 would be negatively influenced by the presence of a second therapeutic agent. Thus, the objection that a skilled person would not be able to carry out the invention defined in claim 1 in respect of devices containing more than one active ingredient

is based purely on speculative considerations and is therefore not convincing.

1.2 A further objection raised by the appellants concerns the ageing step defined in claim 7. The appellants argue that since this step is carried out at 15-30°C, it will not stop after 40 days as required in claim 1 if the device is stored at room temperature.

1.2.1 In the Board's understanding the ageing process merely consists in storing the intravaginal device at controlled temperature for a specified period of time (see [0055]). There can be no doubt that the skilled person would be able to carry out such a process. In the Board's view, the fact that chemical or physical transformations occurring during the ageing step may continue even after the time range defined in claim 7 if the device is stored at room temperature is a matter that does not concern the requirement of sufficiency of disclosure.

In view of the above the Board concludes that the requirement of sufficiency of disclosure is met.

2. Priority

During the appeal proceedings the parties did not dispute the opposition division's conclusion that the subject-matter of the main request is not entitled to the priority date.

The Board sees no reasons to deviate from this conclusion. Accordingly, document D1, published between the priority date and the filing date of the patent in suit, is a prior-art document pursuant to Article 54(2) EPC.

3. Novelty

3.1 The appellants' objections under Article 54 EPC are based on the disclosures of documents D1 and D2.

3.2 Examples 1 to 8 of document D1 relate to the preparation of an intravaginal device containing metronidazole as active ingredient in an amount which varies between 0.64 and 25.6% (w/w). The preparation of the device involves a curing step of the elastomeric mixture containing metronidazole, carried out at 80°C for 2 minutes. Apart from this step, the process does not include any further step in which the mixture is heated. Hence, these examples do not disclose a process involving a maturing step corresponding to step (iii) of claim 1 of the main request, namely a step in which the elastomeric mixture containing the active ingredient is heated at 40° to 100°C for 2 to 72 hours.

Example 13 of D1 relates to the preparation of a device containing 40% (w/w) of metronidazole. The process involves a curing step and a post-curing step which correspond respectively to steps (ii) and (iii) of claim 1 in suit. The process of this example differs from the method of claim 1 of the main request in that the amount of active ingredient is more than 30% (w/w).

3.2.1 The appellants argue that the teaching of example 13 with regard to the post-curing step also applies to examples 1 to 8 of D1, with the effect that these examples also incorporate a step of post-curing equivalent to the maturing step of claim 1.

3.2.2 The Board does not share this position. The sole reference in D1 to a post-curing step is in the context of preparation of the device of example 13. There is no

indication that this step should also be carried out in the preparation of other devices. Thus, document D1 fails to disclose a process combining the curing step of examples 1 to 8 with the post-curing step of example 13.

Hence, the opposition division was correct in its conclusion that D1 does not disclose a device containing less than 30% of a therapeutic agent and prepared in a process comprising a maturing step as defined in step (iii) of claim 1.

3.3 In their arguments in support of the novelty attack based on document D2, the appellants bring together various paragraphs of this document without pointing to any specific example or passage disclosing a process combining all the features recited in claim 1 of the main request. They refer in particular to a passage of column 2 (line 14) disclosing the feature "less than 30%" and to a passage of column 7 (lines 3 to 4) disclosing a vulcanisation step of 1 to 6 hours at a temperature of 60°C to 120°C.

3.3.1 The Board notes that the passage of column 2 mentioned by the appellants is part of the "Background of the invention" section and therefore does not relate to the devices of D2. In any case, there is no link in D2 between this passage and the paragraph of column 7 concerning the vulcanisation step. Furthermore, this paragraph of column 7 does not refer to any particular drug, and the general disclosure of D2 is not limited to devices containing a drug having a solubility in silicone oil at 25°C of less than 0.1 mg/ml as required by claim 1.

Hence, document D2 fails to provide a clear and unambiguous disclosure of a method for preparing an intravaginal drug delivery device having all the features of the method defined in claim 1 of the main request.

3.4 The method of claim 1 is therefore novel over the disclosures of documents D1 and D2.

4. Inventive step

4.1 The invention underlying the patent in suit relates to a process for preparing an intravaginal matrix drug delivery device.

4.2 Closest prior art

The Board agrees with the parties in considering document D1 as the closest prior art.

As discussed in point 3.2 above, examples 1 to 8 of document D1 disclose a method for preparing intravaginal devices containing metronidazole as active ingredient. The process of claim 1 of the main request differs from the methods of examples 1 to 8 of D1 mainly in that it comprises a maturing step (step (iii)).

4.3 Technical problem

4.3.1 Example 5 of the patent shows that the day-1 release rate of a device containing less than 30% of acyclovir as therapeutic agent and prepared by a process comprising a maturing step is higher than the day-1 release rate of a device having the same composition

but prepared by a process which does not comprise a maturing step (see paragraph [0071]).

Thus, this example illustrates the technical effect arising from the introduction of a maturing step after a curing step in the process of manufacturing an intravaginal device.

4.3.2 The appellants' argument that this example does not establish whether any effect is associated with the amount of active ingredient does not appear relevant in the present case.

The device of claim 1 differs from the devices of examples 1 to 8 of D1 in that it is prepared by a process comprising a maturing step. What matters in defining the technical problem is primarily to establish the technical effects caused by the distinguishing feature. The experiment described in example 5 compares the day-1 drug release of devices prepared by a process comprising a maturing step with the day-1 drug release of devices which are identical to the first ones, except for the fact that they are prepared by a process in which no maturing step has been carried out. Thus, in the Board's view, the experiment of example 5 is correctly designed to allow assessment of the effects arising from the distinguishing feature.

In any case, the Board notes that the patent also provides experimental data concerning devices containing more than 30% of active ingredient, i.e. devices excluded by the scope of claim 1 (see e.g. examples 1 and 2). The data show that in these cases the effect of the presence of a maturing step in the manufacturing process is to reduce the day-1 drug

release rate. Thus, these results, together with the results of example 5, provide experimental support for the teaching of the patent according to which, when the drug loading of the device is below 30%, the presence of a maturing step increases the day-1 release rates, while the contrary happens when the drug loading is above 30% (see paragraphs [0014] and [0015]).

4.3.3 In view of the considerations set out above, the Board formulates the technical problem as the provision of a process for producing an intravaginal device containing less than 30% of active ingredient wherein said device provides an increase of the day-1 release rates.

4.4 Obviousness

4.4.1 As discussed in point 3.2 above, example 13 of D1 relates to intravaginal devices containing 40% of metronidazole. Some of these devices are prepared by a manufacturing process which includes a post-curing step, equivalent to the maturing step (iii) of claim 1 in suit. According to example 13, the post-curing step improves the mechanical and release characteristics of the device (page 29, lines 27 to 30).

In the appellants' opinion, the skilled person would deduce from the teaching of example 13 that the day-1 release rates of the devices of examples 1 to 8 could be increased by modifying the manufacturing process with the addition of a post-curing step (*i.e.* maturing step). However, the experimental data disclosed at the end of example 13 of D1 (page 30, lines 1 to 20) show that the metronidazole devices prepared by a process which does not include a post-curing step have a day-1 release rate of 82.9 mg/day, while the metronidazole devices prepared by a process including a post-curing

step at 60°C or a post-curing step at 60°C and storage at controlled temperature for 3 weeks have release rates of respectively 74.4 mg/day and 70.5 mg/day. Hence, in the experiment of example 13 the effect of a post-curing step is to reduce the day-1 release.

Thus, the sentence on page 29 of example 13 according to which the post-curing step improves the release characteristics of the devices would not be regarded by the skilled person as an indication that the day-1 release rates of the devices are increased by performing a post-curing step. Such a reading of this sentence of example 13 would be against the experimental data provided in the example itself.

Since D1 does not provide any other teaching in relation to the effect of a post-curing (maturing) step, the Board concludes that this document does not suggest modifying the manufacturing process of the devices of examples 1 to 8 by the addition of a maturing step as a measure to increase the day-1 release rates of these devices. On the contrary: the results disclosed in example 13 would rather suggest that a maturing step is to be avoided because it could reduce the day-1 release rates of the devices.

4.4.2 In the appellants' opinion, the teaching of document D11 would suggest to the skilled person to perform a maturing step in order to increase the day-1 release rates.

D11 is an article in which the authors review the factors that may lead to a burst effect in controlled release systems. In the Board's view, the aim of this document is not to suggest technical measures that

could be used to obtain a burst effect. Indeed, it is explained on page 122 (right-hand column, first complete paragraph) that burst release is unpredictable and, even when desired, the amount of burst cannot be significantly controlled. The purpose of D11 appears therefore to be to explain which phenomena may cause a burst effect without teaching how these phenomena could be controlled in order to obtain an increase in the day-1 release. Thus, for this reason alone the Board doubts that the skilled person confronted with the present technical problem would consider document D11 as a relevant source of information.

4.4.3 The paragraph of D11 referred to by the appellants (page 124, paragraph 3.3.1) indicates that during drying and storage steps the drugs can migrate. This may result in a heterogeneous distribution in the device and may lead to burst release. However, as observed by the respondent, this passage of D11 relates to hydrogel systems. Indeed, in the sentence linking the left and right-hand columns of D11 it is explained that the migration of drugs may occur during the drying process as the water moves to the gel surfaces and evaporates. Reference to hydrogel systems is also made in the description of figures 3 and 5 of D11 (pages 124 and 125). In contrast, document D1 is concerned solely with devices formed from elastomers. Hydrogel systems are explicitly excluded (page 4, lines 25 to 30). Hence, the skilled person would have no reason to consider the teaching of paragraph 3.3.1 of D11 in the context of the devices of D1.

Thus, the skilled person facing the technical problem defined in 4.3.3 above would not find any relevant suggestion in D11.

4.5 In view of the above, the Board concludes that the claims of the main request meet the requirements of Article 56 EPC.

5. Clarity

5.1 The appellants support their objection against the clarity of claim 1 with the argument that the subject-matter of this claim is defined as a result to be achieved. However, they do not establish any link between this objection and amendments to claim 1 occurring after the grant of the patent. Nor can the Board observe problems of clarity arising from amendments to the claims as granted.

Hence, since there are no issues of clarity introduced by amendments to the patent, claim 1 may not be examined for compliance with Article 84 EPC (see G 3/14, OJ EPO 2015, A102).

5.2 The same conclusion applies to the objections under Article 84 EPC against claims 4 to 8. The considerations set out by the appellants in respect of these claims (see point VIII (d) above) would equally apply to granted claims 6 to 10, which are nearly identical to claims 4 to 8 of the main request. None of the alleged problems of clarity arises out of amendments made after the granting of the patent. Thus, claims 4 to 8 may likewise not be examined for compliance with Article 84 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar: The Chairman:

S. Fabiani I. Beckedorf

Decision electronically authenticated