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Datasheet for the decision of 15 November 2021

Case Number: T 0179/16 - 3.3.07

Application Number: 11162857.4

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Language of the proceedings: EN

Title of invention:
Sustained release small molecule drug formulation

Patent Proprietor:
Durect Corporation

Opponent:
Generics [UK] Limited

Headword:
Sustained release risperidone formulation / DURECT

Relevant legal provisions:
EPC Art. 100(a), 56, 76(1), 123(2)

Keyword:
Inventive step - main request, auxiliary requests 1-2 (no) - auxiliary request 4 (yes)
Divisional application - added subject-matter (auxiliary request 3: yes, auxiliary request 4: no)

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Case Number: T 0179/16 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 15 November 2021

Appellant: (Opponent)	Generics [UK] Limited (trading as Mylan) Albany Gate Darkes Lane Potters Bar Hertfordshire EN6 1AG (GB)
Representative:	Elkington and Fife LLP Prospect House 8 Pembroke Road Sevenoaks, Kent TN13 1XR (GB)
Respondent: (Patent Proprietor)	Durect Corporation 10260 Bubb Road Cupertino, CA 95014 (US)
Representative:	J A Kemp LLP 80 Turnmill Street London EC1M 5QU (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 27 November 2015 rejecting the opposition filed against European patent No. 2361609 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	E. Duval
	Y. Podbielski

Summary of Facts and Submissions

I. European patent 2 361 609 (hereinafter "the patent") was granted from the divisional application 11162857.4. The parent application was published under the PCT as WO 2007/041410 A2. Claim 1 of the patent read as follows:

"An injectable depot formulation, comprising:
a biocompatible polylactide which is a polymer based on lactic acid or a copolymer based on lactic acid and glycolic acid, wherein the polylactide has a monomer ratio of lactic acid to glycolic acid of from 100:0 to 15:85 and wherein the polylactide has a number average molecular weight of 1,000 to 30,000;
an organic solvent combined with the biocompatible polymer to form a viscous gel; and
risperidone, in base or salt form, incorporated in the viscous gel."

II. An opposition was filed against the patent on the grounds that its subject-matter lacked inventive step, it was not sufficiently disclosed and it extended beyond the content of the (parent) application as filed.

III. The opposition division took the decision to reject the opposition filed against the patent.

The decision cited in particular the following documents:

D1: WO 2005/048989 A1
D3: EP 1 210 942 A2

D4: Hatefi & Amsden (2002) Journal of Controlled Release 80, 9-28. Biodegradable injectable in situ forming drug delivery systems

IV. The opposition division decided in particular that:

(a) The patent as granted complied with the requirements of Articles 123(2) and 76(1) EPC. Neither the combination of features pertaining to the polylactide monomer ratio and number average molecular weight and the choice of risperidone, nor the omission of the features regarding the release profile, represented added subject-matter.

(b) The patent as granted met the requirements of sufficiency of disclosure.

(c) Regarding inventive step, D3 was selected as the closest prior art rather than D1, because D1 failed to disclose any specific formulation comprising risperidone as the active ingredient.

D3 disclosed an injectable polylactide polymer microparticle formulation which provided a sustained release of risperidone. The subject-matter of claim 1 of the patent differed from D3 in that it related to an injectable viscous gel and in the molecular weight of the polylactide, i.e. 1,000 to 30,000. The problem to be solved was regarded as the provision of an alternative injectable formulation of risperidone which provided sustained release *in vivo*. The claimed solution was not obvious in light of D4 or D1. Consequently, the patent as granted met the requirements of inventive step.

V. The opponent (appellant) lodged an appeal against the decision of the opposition division.

VI. In its reply to the appeal, filed on 12 August 2016, the patent proprietor (respondent) defended its case on the basis of the patent as granted as the main request, and submitted auxiliary requests 1-12.

Claim 1 of auxiliary request 1 was identical to claim 1 as granted.

In claim 1 of auxiliary request 2, the range for the polylactide number average molecular weight was amended to 5000-30000.

Claim 1 of auxiliary request 3 specified that the risperidone, in base or salt form, has less than 1 mg/ml solubility in water.

Claim 1 of auxiliary request 4 combined the amendments of auxiliary request 2 and 3.

VII. The appellant filed further submissions with its letter dated 6 March 2017.

VIII. The following documents, among others, were submitted by the parties during the appeal proceedings:

A009: Wang et al., Structure formation in injectable poly(lactide-co-glycolide) depots, Journal of Controlled Release 90 (2003), 345-354
A010: Wang et al., Drug release from injectable depots: two different in vitro mechanisms, Journal of Controlled Release 99 (2004), 207-216.
A011: US 2005/0079202 A1

A012: US 2005/0106214 A1
A013: Extracts from the European Pharmacopoeia, 5th Edition, published 15 June 2004
A014: Experimental Report prepared by Dr Jeremy C. Wright, 10 August 2016

IX. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA issued on 28 July 2020.

X. By letter dated 15 September 2021, the appellant withdrew its request for oral proceedings.

XI. By letter dated 10 November 2021, the respondent submitted new auxiliary requests 7-12, the previous auxiliary requests 7-12 filed on 12 August 2016 being renumbered auxiliary requests 13-18.

XII. Oral proceedings were held before the Board on 15 November 2021 in the presence of the respondent.

XIII. The arguments of the appellant may be summarized as follows:

(a) Added subject-matter

Claim 1 of the main request omitted the essential *in vivo* release profile defined in claim 1 and paragraphs [0005] and [0006] of the parent application as filed. The omission of the release profile could not be based on paragraph [0013] of the parent application as filed, because this paragraph merely described a discovery upon which the invention, defined by reference to this specific release profile, was based. The omission of the feature could not be based on the examples either, because the skilled person would understand that these

were comparative examples. Hence the requirements of Article 76(1) EPC were not met.

Furthermore, starting from the parent application as filed, claim 1 of the main request resulted from the combination of a monomer ratio selected from four alternatives (see paragraph [0017]), a molecular weight range selected from six possible combination of end points (see paragraph [0017]), and an active ingredient selected from at least four options (see paragraph [0020]). The subject-matter thus individualised was not directly and unambiguously derivable from the parent application as filed.

(b) Inventive step

D3 related to a different type of formulations and a different purpose/effect, and thus was not the closest prior art. Rather, D1 represented a suitable starting point for the assessment of inventive step. D1's purpose was to provide desirable release rates (see [0012]). D1 related to injectable depot formulations comprising a beneficial agent, including, in one specifically disclosed option, risperidone (see paragraph [0087]), a biocompatible polymer and a solvent (see claim 1). The polymer could be a copolymer of lactic acid and glycolic acid having a molecular weight of 3000 to 120000, and having a lactic to glycolic acid ratio of between 100:0 to 50:50.

The distinguishing feature was the molecular weight of 1000 to 30000. There was not evidence that this selected molecular weight range provided any technical effect. Consequently, the objective technical problem was the provision of an alternative risperidone formulation. The selection of the lower end of the

molecular weight range of D1 did not involve an inventive step.

Even starting from D3 as closest prior art, the claimed subject-matter still lacked an inventive step. D3 disclosed a microparticle formulation comprising risperidone (see claims 1 and 6). The distinguishing feature was the use of the injectable depot formulation comprising the excipients defined by the patent. The objective technical problem was the provision of an alternative formulation of risperidone.

The claimed solution did not involve an inventive step in light of D1, which showed injectable depot formulations. It had not been established that a prejudice existed against the use of risperidone in a depot gel formulation. Alternatively, the claimed solution was obvious in light of the review article D4, describing depot gel formulations comprising a water soluble polylactide polymer and a solvent, or in light of A009-A012.

Thus the subject-matter of claim 1 of the main request did not involve an inventive step.

The limitation of the polylactide molecular weight to 5000-30000 (auxiliary requests 2 and 4) did not change any of the issues. The solubility of risperidone or its salt specified in claim 1 of auxiliary requests 3 and 4 merely defined a physical property of risperidone and therefore did not distinguish the claimed subject-matter from D1.

XIV. The arguments of the respondent may be summarized as follows:

(a) Added subject-matter

The omission, in claim 1 of the main request, of the release profile ("an *in vivo* release profile having C_{max} to C_{min} ratio less than 200 and lag time less than 0.2") did not infringe Article 76(1) EPC, because this feature was not indicated to be essential or indispensable in the parent application as filed. Paragraph [0013] of the parent application disclosed that it was the incorporation of the drug in the depot gel vehicle that solved the problem of achieving near zero-order release. The working examples confirmed that this problem could be solved without the feature at issue. Furthermore, the omitted release profile feature did not specify the time period within which the C_{min}, C_{max} and T_{lag} were measured, such that this feature was not limiting.

The polylactide according to claim 1 of the main request, having a lactic acid to glycolic acid monomer ratio of 100:0 to 15:85 and a molecular weight of 1000 to 30000, was disclosed as a preferred compound in paragraph [0017] of the parent application. The skilled person would have understood that such a polylactide could be used with risperidone, such that the combination of features of claim 1 was implicitly disclosed in the application as filed.

Hence the main request complied with Article 76(1) EPC.

(b) Inventive step

The invention related to formulations of risperidone, which was known to be insoluble in water (see A013). The effect of incorporating risperidone in the claimed

formulation was a near zero order release, as shown by the example (see formulations 63 and 73, figure 2).

It was not contested that D1 was suitable as a starting point for the assessment of inventive step. The subject-matter of claim 1 of the main request differed from the teaching of D1 by the combination of risperidone with a polylactide having the claimed monomer ratio and molecular weight. The technical problem was to provide risperidone formulations having near zero order release *in vivo*.

D1 broadly described injectable depot gel compositions for sustained delivery of beneficial agent, and only referred to risperidone in a vast and speculative list of possible beneficial agents (see paragraphs [0085]-[0089]). D1 only contained evidence of a sustained release in respect of water soluble drugs. Furthermore, the nature of a drug was known to have an important effect on release profile from these formulations. D1 did not make it plausible that a sustained release could be achieved with water insoluble drugs, or with risperidone, irrespective of its form or solubility. Likewise, neither D4 nor A009-A012 led to the claimed subject-matter.

Thus the main request met the requirements of inventive step.

XV. The appellant requests that the decision under appeal be set aside and that the patent be revoked.

XVI. The respondent requests that the appeal be dismissed and the patent be maintained as granted or, alternatively, that the case be remitted to the opposition division for consideration of one of

auxiliary requests 1-18, wherein auxiliary requests 1-6 were filed with letter dated 12 August 2016, auxiliary requests 7-12 were filed with letter dated 10 November 2021, and auxiliary requests 13-18 had been filed as auxiliary requests 7-12 with letter dated 12 August 2016. The respondent also requests that the Board consider auxiliary requests 1-18 in the event that the main request and the request for remittal are refused.

Reasons for the Decision

1. Main request (patent as granted), inventive step

1.1 The claimed invention relates to injectable depot formulations of risperidone. According to the patent, the problem underlying the invention is to address the issues associated with plasma concentration peaks and troughs observed with oral pills and bolus injections and to provide a sustained, near zero-order release dosage form of the drug designed to minimize variations in plasma concentration following dosing (see paragraphs [0003]-[0004] and [0013]).

1.2 D1 has similar objectives. D1 (see paragraphs [0004]-[0008] and [0012]) addresses the issue of modulating the release of beneficial agents from drug delivery systems to achieve desirable or sustained release rates, and mentions the problems of bursts or lag time in the delivery of the beneficial agent. Claim 1 of D1 pertains to injectable depot formulations comprising, among others, a beneficial agent, a biocompatible polymer and a solvent. Although the formulations exemplified in D1 comprise different beneficial agents (namely bupivacaine and hGH), risperidone (erroneously spelled "resperidone" in paragraph [0087]) is mentioned

in D1 among a long list of beneficial drugs to be used in the formulations. In one alternative of D1 (see claims 22-24), the polymer comprises a copolymer of lactic acid and glycolic acid (PLGA) having a weight average molecular weight of 3000 to 120000 and a monomer ratio of lactic acid to glycolic acid between 100:0 and 50:50.

Accordingly, D1 represents a suitable starting point for the assessment of inventive step. This was accepted by the respondent during the oral proceedings before the Board.

1.3 The Board agrees with the appellant that the starting point within D1 is the disclosure of an injectable depot formulations comprising risperidone, a biocompatible polymer and a solvent, since this direct and unambiguous disclosure results from the single selection of the active agent within D1. This is also the disclosure coming closest to the claimed subject-matter, considering that the nature of the active agent is an essential aspect in the development of formulations having desirable release properties. D1 does not, however, show this risperidone composition in combination with the selection of PLGA having a number average molecular weight of 1000 to 30000.

1.4 The respondent did not assert that the choice of the excipients or polymer from among those disclosed in D1 was associated with any particular technical effect. Rather, the respondent argued that risperidone was known to be insoluble in water, whereas D1 did not provide evidence of any sustained release profile for compositions comprising active agents other than water soluble drugs. Thus, according to the respondent, the patent would demonstrate that the incorporation of

risperidone in the claimed formulation achieved a sustained, near zero-order release (see paragraph [0013] and figure 2, formulations 63 and 73). This effect would not be plausible from the teaching of D1.

1.4.1 In the Board's opinion, D1 generally states that the depot gel compositions disclosed therein allow the sustained release of any beneficial agent (see 1.2 above). The Board concurs with the respondent that the examples of D1, pertaining to bupivacaine and hGH only, provide limited support for this broad statement. Furthermore, several passages in D1 are consistent with the respondent's view that the skilled person reading D1 would realistically expect such a sustained release only for water soluble drugs (see paragraph [0089], last two sentences, and paragraph [0085]).

1.4.2 However, claim 1 of the main request is not limited to water soluble forms of risperidone. Although risperidone base is known to be practically water insoluble (see A013, page 2374), claim 1 covers any salt thereof, and consequently does not exclude salts having a substantially higher water solubility. It is well known, and confirmed by D1 (see paragraph [0039]), that the hydrophilic-hydrophobic property of a drug can be tailored by its chemical form.

Accordingly, the respondent's arguments based on a reading of D1 as limited to water soluble entities cannot succeed since such entities are allowed by claim 1 of the main request. The subject-matter of claim 1 of the main request as a whole is not characterised by any technical effect which would not be expected to arise in light of D1.

1.5 The objective technical problem is thus the provision of further risperidone compositions.

1.6 The claimed solution consists in selecting a polylactide having a number average molecular weight (namely 1000 to 30000) which, for the most part, is subsumed by the range proposed in D1 (namely 3000 to 120000). This selection does not, in the absence of any associated effect, involve an inventive step.

1.7 The respondent's further arguments based on the review article D4 do not modify this conclusion. D4 emphasises some disadvantages of certain biodegradable injectable *in situ* forming drug delivery systems, or, generally, the release profile's dependence on the nature of the drug incorporated (see point 4.1, page 15, right hand column; page 17, right hand column). However, D4 is not concerned with the teaching of D1 or the possibility to apply it to risperidone.

1.8 Likewise, the respondent's further arguments based on A014 do no affect the present issue. A014 pertains to another, water soluble active ingredient, namely amitriptylene HCl. This post-published evidence A014 neither demonstrates an effect associated with the claimed risperidone compositions, nor invalidates the conclusion that the skilled person, reading D1, would in general expect a sustained release from compositions comprising water soluble drugs.

In conclusion, the main request does not meet the requirements of Article 56 EPC.

2. Auxiliary requests, remittal to the opposition division

The respondent requested, in case the Board did not allow the main request, that the case be remitted to the opposition division for consideration of the auxiliary requests.

Pursuant to Article 11 RPBA 2020, the Board shall not remit a case to the department whose decision was appealed for further prosecution, unless special reasons present themselves for doing so. In the present case, no such special reasons were identified by the respondent. The opposition division took a decision *inter alia* on inventive step and added subject-matter, and at least auxiliary requests 1-4 do not significantly change the scope of the appeal proceedings. Hence the Board decided not to remit the case to the opposition division for further prosecution.

3. Auxiliary requests 1 and 2, inventive step

3.1 Since claim 1 of auxiliary request 1 is identical to claim 1 of the main request, the finding of lack of inventive step applies to auxiliary request 1.

3.2 Claim 1 of auxiliary request 2 limits the number average molecular weight of the polylactide to 5000 to 30000. This range does not depart from the broader range of molecular weights disclosed in the closest prior art D1, namely 3000 to 120000. Accordingly, auxiliary request 2 infringes Article 56 EPC for the same reasons as for the main request.

4. Auxiliary request 3, Article 76(1) EPC, combination of the features of claim 1

4.1 The injectable depot formulation of claim 1 of auxiliary request 3 comprises - as does claim 1 of the main request - in particular, a polylactide having a number average molecular weight of 1000 to 30000, and risperidone, in base or salt form. For the following reasons, the Board comes to the conclusion that the parent application as filed provides no basis, for the purposes of Article 76(1) EPC, for the combination of these features.

4.2 The claimed molecular weight range 1000-30000 results from a combination of the general range of 1000-120000 with the preferred range of 5000-30000 disclosed in paragraph [0017] of the parent application as filed. This combination of the general lower limit with the preferred upper limit does not *per se* introduce added subject-matter. However it must be seen as a first selection out of the various ranges which may be created from the general and preferred ranges.

Furthermore, the small molecule drug has been limited to one of the two drugs recited in claim 11, namely base and salt forms of R209130 and risperidone. Paragraph [0020] and the examples of the parent application as filed also recite several small molecule drugs including R209130 (base, mandelic acid salt and tartaric acid salt) and risperidone (base and pamoate). Risperidone is not identified as preferred over R209130 in the parent application as filed.

4.3 The respondent did not convincingly show that the parent application contained any pointer to the claimed combination. The argument that the combination range 1000-30000 would be more preferred than the general range 1000-120000 because it includes the preferred range 5000-30000 cannot be accepted, as any such

preference would only apply to the 5000-30000 part. Since the parent application as filed does not point to the combination of risperidone with the combination range including the lower end point of 1000, the Board concludes that the subject-matter of claim 1 of auxiliary request 3 does not derive, directly and unambiguously, from the parent application as filed.

Accordingly, auxiliary request 3 does not meet the requirements of Article 76(1) EPC.

5. Auxiliary request 4

5.1 Articles 123(2) and 76(1) EPC

5.1.1 Claim 1 of auxiliary request 4 combines a monomer ratio of 100:0 to 15:85 (i.e. the broadest ratio of paragraph [0017] in the parent application as filed), a number average molecular weight of 5000 to 30000 (disclosed as preferred in paragraph [0017] in the parent application as filed), and the small molecule drug risperidone (selected from the preferred drugs in the parent application as filed). As emphasised by the respondent, this preferred molecular weight range encompasses the polylactides used in all examples, which have molecular weights ranging from 6400 to 16000. Apart from the choice of risperidone as active agent, the Board does not view the above combination of features in claim 1 of auxiliary request 4 as resulting from multiple selections or as adding subject-matter. Furthermore, the feature that the risperidone, in base or salt form, has less than 1 mg/ml solubility in water is disclosed as preferred in paragraph [0019] of the parent application as filed.

5.1.2 In the parent application as filed, the invention is defined in claims 1 and 17, and paragraphs [0005] and [0006], by the feature that "the formulation exhibits an *in vivo* release profile having C_{max} to C_{min} ratio less than 200 and lag time less than 0.2". In contrast, claim 1 of auxiliary request 4 does not comprise this feature.

The Board shares the opinion of the respondent that the omission of this feature does not infringe Article 76(1) EPC, because it is not indicated to be essential or indispensable in the parent application as filed. To the contrary, paragraph [0013] discloses that it is the incorporation of the drug in the depot gel vehicle that solves the technical problem of achieving a near zero-order release. The last sentence of paragraph [0013] also indicates that "several small drug formulations have been identified in this invention" with *in vivo* release profiles having a C_{max} to C_{min} ratio less than 200 and lag time less than 0.2. The use of the word "several" supports the view that the invention is not limited to these identified small drug formulations. Furthermore, the parent application as filed contains several examples having lag time T_{lag} above 0.2 (see example 5, paragraph [0030]) or C_{max}/C_{min} above 200 (see formulation 63 in table 3, which nonetheless has a near zero order release profile similar to formulation 73 in figure 2). None of these examples are identified as reference examples. Accordingly, taking into account paragraph [0013] and the examples, it is directly and unambiguously derivable from the parent application as filed that the omitted *in vivo* release profile is not essential to the invention.

5.1.3 In conclusion, auxiliary request 4 meets the requirements of Article 76(1) EPC. Since the divisional

application as filed includes the same disclosure as the parent application as filed, the requirements of Article 123(2) EPC are also met.

5.2 Inventive step

5.2.1 Starting from the injectable depot formulations of D1 (see 1.2 and 1.3 above) comprising risperidone, a biocompatible polymer and a solvent, the subject-matter of claim 1 of auxiliary request 4 differs not only by the choice of the polylactide having a number average molecular weight of 5000 to 30000 but also in that the risperidone, in base or salt form, has less than 1 mg/mL solubility in water. Accordingly, the claimed subject-matter is limited to formulations for which D1 does not credibly demonstrate any sustained release (see 1.4.1 above).

5.2.2 The patent demonstrates that the formulations of claim 1 of auxiliary request 4 achieve, qualitatively, a sustained or near zero-order release for a duration of about 10 days (see figure 2, formulations 63 and 73). The respondent defines the technical problem as the provision of a risperidone formulation having near zero order release *in vivo*. The Board concurs.

5.2.3 The skilled person reading D1 would not consider the claimed formulations, comprising water insoluble forms of risperidone, as a solution to the problem of providing a sustained release (see also 1.4.1 above). The skilled person would not be led to the claimed invention by the review article D4 either. D4 describes depot gel formulations comprising a water soluble polylactide polymer and a solvent, but does not pertain to risperidone (see 1.7 above).

5.2.4 The Board does not regard the appellant's objection starting from D3 to be convincing either.

D3 discloses pharmaceutical compositions comprising controlled release microparticles having improved shelf-life, said microparticles comprising active agents encapsulated within a polymer matrix. D3 is not concerned with the release profile of said microparticle compositions, but rather aims at reducing degradation by reducing the levels of residual processing solvent (see [0001] and [0007]). In some examples, D3 shows a polylactide polymer microparticle formulation which comprises risperidone.

5.2.5 To the extent that D3 may qualify as a starting point for the assessment of inventive step, the claimed formulations differ from those of D3 at least by the use of the injectable depot formulation comprising the excipients defined in claim 1. For the reasons set out above (see 5.2.2), the technical problem is the provision of an injectable formulation of risperidone providing sustained release *in vivo*.

5.2.6 As explained above, neither D1 nor D4 allow the skilled person to expect a sustained release from the claimed formulations comprising risperidone with low water solubility. The same is true of A009-A012. A009 (see pages 345-346) and A010 mention some advantage of some gel depot formulations, such as a stabilization of macromolecules and a long lasting delivery profile without initial burst, in particular with a polylactide falling within the scope of claim 1 (50/50 PLGA with a molecular weight of 12000 to 20000). However there is no indication in A009 or A010 that any such long lasting delivery profile would also arise with risperidone having low water solubility.

A011 and A012 are similar to D1, in that they disclose gel depot formulations wherein the beneficial agent may be risperidone and the polymer a polylactide (see A011, abstract and paragraphs [0101] and [0143]; A012, abstract and paragraphs [0020] and [0093]). But they are similar to D1 also in their speculative nature and lack of evidence regarding the risperidone with low water solubility of claim 1. Thus A011 and A012 do not modify the above conclusion.

Accordingly, auxiliary request 4 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 Opposition Division with the order to maintain the patent on the basis of auxiliary request 4 filed with letter dated 12 August 2016 and a description to be adapted thereto.

The Registrar: The Chairman:

B. Atienza Vivancos A. Usuelli

Decision electronically authenticated