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Case Number: T 1895/23 - 3.3.07

Application Number: 17183851.9

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Title of invention:
SULFOALKYL ETHER CYCLODEXTRIN COMPOSITIONS

Applicant:
CyDex Pharmaceuticals, Inc.

Headword:
Sulfoalkyl ether cyclodextrin compositions / CYDEX

Relevant legal provisions:
EPC Art. 56

Keyword:
Inventive step - (no)

Decisions cited:
T 0764/12, T 0142/06, T 0007/18

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Boards of Appeal

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Case Number: T 1895/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 11 March 2025

Appellant: (Applicant)	CyDex Pharmaceuticals, Inc. 5980 Horton Street Suite 405 Emeryville, CA 94608 (US)
Representative:	Harris, Jennifer Lucy Kilburn & Strode LLP Lacon London 84 Theobalds Road London WC1X 8NL (GB)
Decision under appeal:	**Decision of the Examining Division of the European Patent Office posted on 4 May 2023 refusing European patent application No. 17183851.9 pursuant to Article 97(2) EPC.**

Composition of the Board:

Chairman	D. Boulois
Members:	E. Duval
	A. Jimenez

Summary of Facts and Submissions

I. The appeal was filed by the applicant (appellant) against the decision of the examining division to refuse the patent application in suit.

II. The decision was based on the main request and auxiliary requests 1-7 filed on 28 February 2023.

Claim 1 of the main request read as follows:

"A process for preparing a sulfoalkyl ether cyclodextrin (SAE-CD) composition, the process comprises:
(a) mixing in an aqueous medium a cyclodextrin with a sulfoalkylating agent in the presence of an alkalizing agent to form an aqueous reaction milieu comprising a sulfoalkyl ether cyclodextrin, one or more unwanted components, and one or more drug-degrading impurities;
(b) conducting one or more separations to remove the one or more unwanted components from the aqueous milieu to form a partially purified aqueous solution comprising the sulfoalkyl ether cyclodextrin and the one or more drug-degrading impurities, wherein the one or more separations include a process selected from: ultrafiltration, diafiltration, centrifugation, extraction, solvent precipitation, and dialysis; and
(c) repeatedly treating the partially purified aqueous solution with a phosphate-free activated carbon to provide the SAE-CD composition comprising the sulfoalkyl ether cyclodextrin and less than 100 ppm of a phosphate, wherein the repeated treating comprises passing and recycling the partially purified aqueous solution through a mass of phosphate-free activated carbon in a flow-through apparatus until the amount of

drug-degrading agent in the solution is reduced to a target level, wherein the SAE-CD composition has an absorption of less than 0.5 A.U. due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution containing 300 mg of the SAE-CD composition per mL of solution in a cell having a 1 cm path length; and
wherein the activated carbon is granular."

In claim 1 of auxiliary request 2, the UV absorption was amended to "less than ~~0.5~~ 0.25 A.U." for "an aqueous solution containing ~~300~~ 500 mg of the SAE-CD composition per mL of solution" (amendments emphasised by the Board).

Claim 1 of auxiliary request 4 corresponded to claim 1 of the main request with the addition of the following features:
"wherein the repeated treating comprises passing and recycling the partially purified aqueous solution through the mass of phosphate-free activated carbon two or more times, wherein each passing is with a different mass of activated carbon; and
wherein the activated carbon is granular"

III. The following documents were cited in the appealed decision:

D11: US 6 153 746 A
D13: US 5 569 756 A
Annex A: Declaration of Dr. Antle (A) dated 26 March 2013
Annex B: Declaration of Dr. Antle (B) dated 27 February 2023

IV. The examining division decided that none of the requests satisfied the requirements of inventive step.

Starting from D11 as the closest prior art, the process of claim 1 of the main request differed in that:
a) a flow through apparatus was used;
b) granular carbon was used;
c) treatment with activated carbon was repeated in a flow through apparatus
d) until the amount of drug-degrading agent in the solution was reduced to a target level, wherein the SAE-CD composition had an absorption of less than 0.5 A.U. due to a drug-degrading agent; and
e) the carbon was phosphate free.
The technical problem was possibly to provide a process which avoided the filtration step for producing SAE-CD compositions that had an improved purity and may lead to a lower risk of drug degradation. The solution did not involve an inventive step in light of D13 in particular.

Likewise, each of the auxiliary requests 1-7 infringed Article 56 EPC.

V. With their statement setting out the grounds of appeal, the appellant re-submitted the same main request and auxiliary requests 1-7.

VI. The Board set out its preliminary opinion in a communication under Article 15(1) RPBA.

VII. By letter dated 4 March 2025, the appellant filed auxiliary requests 8-15.

VIII. Oral proceedings were held before the Board by videoconference. During the oral proceedings, the

appellant withdrew all requests except the main request, auxiliary request 2 and auxiliary request 4 (see II. above).

IX. The appellant requests that the decision under appeal be set aside and that a patent be granted on the basis of the main request or, in the alternative, on the basis of one of auxiliary requests 2 or 4, as submitted to the examining division on 28 February 2023 and filed again with the statement setting out the grounds of appeal.

X. The appellant's argument regarding inventive step may be summarised as follows:

Starting from document D11, the subject matter of claim 1 differed in that:
a) the treatment with activated carbon was carried out through a flow-through apparatus,
b) the activated carbon was granular,
c) the treatment with activated carbon was repeated,
d) the repeated activated carbon treatment was carried out until the SAE-CD composition reached the claimed threshold for purity in relation to a drug-degrading agent as determined by UV/vis spectrophotometry, and
e) the activated carbon was phosphate free.
The objective technical problem was the provision of an improved process that provided both processing benefits and resulted in a product with a beneficial purity profile (i.e. low levels of phosphate and drug-degrading agent).
The claimed solution involved an inventive step because the existence of the particular drug-degrading impurity concerned had not been recognized in D11 or D13, and because neither documents taught a repeated treatment with activated carbon on SAE-CD compositions in a flow-

through apparatus using a phosphate free granular activated carbon, as recited in the claims. The present situation furthermore qualified as a problem invention, because the prior art did not address the problem of unacceptable levels of drug degradation arising when switching to a flow-through apparatus for the activated carbon treatment so as to to obtain processing benefits over the process of D11. The criteria of inventive step were accordingly met.

Reasons for the Decision

1. Main request, inventive step

1.1 The invention pertains to a process for preparing a sulfoalkyl ether cyclodextrin (SAE-CD) composition. SAE-CD compositions are useful for the complexation of drugs so as to allow for increased solubility of the active pharmaceutical ingredient (API) and in some cases increased stability of drugs in aqueous solutions (see paragraph [0002] of the description).

The invention addresses the problem of removing phosphate and drug-degrading impurities and providing a composition that can be readily mixed with an active agent to provide a high-stability formulation (cf. paragraph [0006]).

1.2 The closest prior art D11 also relates to processes for the preparation of SAE-CD compositions with low levels of impurities (see column 1, lines 7 and 8; column 2, lines 9 to 20).

In example 1 of D11, an SAE-CD composition is prepared by a process comprising:
(a) a step of mixing, in an aqueous medium, β-cyclodextrin with a sulfoalkylating agent (1,4-butane sultone) in the presence of an alkalizing agent (NaOH) to form an aqueous reaction milieu;
(b) a separation step wherein the aqueous milieu is subjected to ultrafiltration; and
(c) a purification step in which the obtained aqueous solution is treated with Darco® KB-B (powder) activated carbon (column 7, lines 47-52). In the large scale example 3 of D11, the composition is batch treated with 9% Darco® KB-B activated carbon for two hours before being filtered.

1.3 Differentiating features

1.3.1 According to paragraph [0113] of the application and Dr Antle's first declaration (Annex A, §3), Darco® KB-B is a carbon which was activated with phosphoric acid. The Board accepts that the activated carbon of D11 accordingly does not qualify as phosphate-free in the sense of claim 1 (see also paragraph [0110]), and that this feature thus differentiates the process of claim 1 from that of D11, as reasoned by the examining division (see the appealed decision, point 1.2, differentiating feature e). Additionally, Annex A indicates that, because of the use of a phosphate-containing activated carbon, the process of D11 results in SAE-CD compositions comprising 127-187 ppm phosphate. Thus, the feature of claim 1 that the resulting SAE-CD composition comprises less than 100 ppm of a phosphate also constitutes a difference over D11.

1.3.2 According to the appellant, D11 does not disclose that the repeated treatment is carried out "until the amount

of drug-degrading agent in the solution is reduced to a target level, wherein the SAE-CD composition has an absorption of less than 0.5 A.U. due to a drug-degrading agent, as determined by UV/vis spectrophotometry at a wavelength of 245 nm to 270 nm for an aqueous solution containing 300 mg of the SAE-CD composition per mL of solution in a cell having a 1 cm path length".

The Board agrees that the activated carbon treatment is not repeated in D11. D11 shows a single batch treatment with powdered, phosphate-activated carbon.

However, in the Board's opinion, the target level in drug-degrading agent, defined in claim 1 by reference to a UV/vis absorption at 245-270 nm of less than 0.5 A.U. for a concentration of 300 mg/mL, cannot be assumed to represent a difference over D11. No demonstration was adduced that the single batch treatment with powdered, phosphate-activated carbon of D11 would lead to a composition exceeding the absorption limit of claim 1.

The application compares compositions that underwent either a double treatment (see example 24), wherein the solution is passed (recycled) through a first column then through a second column, each charged with fresh granular, phosphate-free activated carbon, or a single treatment (see example 27), wherein the solution is passed through a single such column. The application further reports UV/vis measurements and the extent of degradation of selected APIs in these solutions (see figures 1 and 2, and examples 28-34). However no UV/vis absorption data regarding the single batch treatment with powdered, phosphate-activated carbon of D11 is given. On the contrary, the appellant indicates that no

such drug degradation was observed with the process of D11 (see §2 of the grounds of appeal). Considering that the claimed UV/vis absorption at 245-270 nm is an unusual parameter, no benefit of the doubt can be given regarding this feature. The amount of drug-degrading agent defined in claim 1 by reference to a UV/vis absorption is thus not regarded as a differentiating feature.

1.3.3 Contrary to the appellant's view, the wording of claim 1 does not imply that the claimed process comprises an actual step of UV measurement. Claim 1 merely defines the SAE-CD composition by the parameter relating to its UV absorption. This requires that a composition falling within the scope defined by this condition be obtained, but not that the process include a step of actually characterising the composition by this particular parameter. The feature that the treatment is repeated until the amount of drug-degrading agent is reduced to a target level does not imply this UV measurement either. Lastly, decision T 7/18 cited by the appellant does not modify this conclusion, as it does not suggest that the impurities levels specified in the claimed process imply a process step of measuring them.

1.3.4 The process of claim 1 thus differs from the teaching of D11 in that it uses a repeated, granular, phosphate-free activated carbon treatment in a flow-through apparatus, and in that the resulting SAE-CD composition comprises less than 100 ppm of a phosphate.

1.4 Technical effects and problem

1.4.1 The Board does not question that the use of phosphate-free activated carbon leads to lower amounts of

phosphate in the resulting SAE-CD composition (see 1.3 above).

1.4.2 The appellant contends that the use of granular phosphate-free activated carbon treatment in a flow-through apparatus provides benefits in terms of processing compared with the process of D11, namely by avoiding the filtration to remove powdered carbon from the batch mixture.

The Board agrees in as far as the powdered carbon filtration step is avoided. The technical effect of avoiding the filtration step can as such be taken into account. This filtration step is however replaced, in a preferred embodiment of claim 1 (see example 27 and claim 2), by a step of passing (recycling) the solution through two or more columns, each charged with (fresh) granular, phosphate-free activated carbon. In other words, the filtration is replaced with several granular carbon column treatment, i.e. as explained by the examining division, it does not lead to fewer steps. In this sense, the modification cannot be more generally regarded as a processing benefit. Furthermore, the fact that the inventive example 24 of the application is carried out on a kilogram scale does not demonstrate an advantage over D11 either, because, as explained by the appellant in their grounds of appeal (see §2), the process described in D11 was already used to produce the marketed product Captisol®, and was hence also amenable to larger scale.

1.4.3 Lastly, the appellant submits that the claimed process results in a product with low levels of drug-degrading impurities. The Board does not consider that any improvement is shown in this respect. As explained above (see 1.3.2), no data is available regarding the

amount in drug-degrading agent or level of UV/vis absorption at 245-270 nm obtained with the single batch treatment with powdered, phosphate-activated carbon of D11. Hence no comparison was adduced to demonstrate any improvement achieved by the claimed process over the closest prior art D11 in this respect.

1.4.4 Accordingly, the objective technical problem is the provision of a process for producing SAE-CD compositions which avoids the filtration step and leads to lower phosphate amounts.

1.5 Obviousness

1.5.1 The use of a column (i.e. a flow-through process) containing granular activated carbon, as an alternative to a batch treatment with powdered carbon, is shown in the context of related cyclodextrin derivatives in D13 (see column 2, lines 42-49; examples 3 and 4). The activated carbon used in D13 is not phosphated (see also column 2, lines 30-41). It is in this respect not relevant that D13 is concerned with different cyclodextrin derivatives or impurities, because the skilled person would understand from D13 that the activated carbon treatment, which is already known from D11, may be performed with a different, alternative technical setup avoiding the need for a filtration. Hence the skilled person, seeking a means to avoid the filtration step, would turn to D13. The Board furthermore agrees with the examining division that the use of phosphate-free carbon to lower the amount of phosphate in the composition does not involve an inventive step (see the appealed decision §1.5.6).

1.5.2 The appellant argues that a previously unrecognised problem was identified, namely drug degradation in drug

products formulated with SAE-CD compositions prepared by a single flow-through treatment using granular, phosphate-free activated carbon.

The Board does not consider that the present situation qualifies as a problem invention. The issue of stability is a general concern with compositions for pharmaceutical use. Additionally, D11 already addresses the issue of purity of the SAE-CD compositions, and uses an activated carbon treatment, not only to remove the starting cyclodextrin as the appellant suggests, but more generally to remove "colours and further reduce any remaining impurities" (see column 6, lines 11-13). The appellant did not contest that the skilled person generally knows that impurities may jeopardize the stability of the active ingredient. Accordingly, the removal of drug-degrading impurities does not represent an unrecognized problem. The posing of this problem cannot represent a contribution to the inventive merits of the solution, since this problem would have been encountered by the skilled person as part of normal development work.

In this, the present situation, where the skilled person, starting from D11 and equipped with common general knowledge, would have been concerned with the removal of potentially drug-degrading impurities, differs from the cases underlying decisions T 7/18 (see point 2.4.6 of the reasons), T 142/06 (see point 5.7 of the reasons) and T 764/12 (see point 4.7.5 of the reasons), where the problem was not hinted at in the prior art.

In addition, the Board does not share the appellant's opinion that the specific nature of the impurities targeted in the present invention amounts to an

unrecognized problem in the prior art. The present application merely correlates the degradation of selected drugs to the claimed UV absorption range, but does not otherwise identify any specific drug-degrading impurities. Claim 1 leaves these impurities as undefined as the drugs they are meant to degrade. In this sense, the problem posed in the application is no more specific than the problem which the skilled person would have considered starting from D11.

The appellant emphasised that this drug degradation problem arises in drug products formulated with SAE-CD compositions prepared by a single flow-through treatment using granular, phosphate-free activated carbon, and that further modifications were accordingly necessary to achieve an improved level of drug degradation. The prior art did not hint at such a modification, namely repeating the treatment.

The Board does not consider this argument to be convincing. Firstly, the technical problem cannot be defined on the basis of a technical effect shown by a comparison, not with the process of the closest prior art D11 (i.e. single batch treatment with powdered, phosphate-activated carbon), but with a worse-performing modified process (i.e. single flow-through treatment using granular, phosphate-free activated carbon). Secondly, the further modification referred to by the appellant actually consists in merely repeating the same impurity-removing carbon treatment. Since D11 already employs a carbon treatment step to remove impurities, an inventive step cannot reside in repeating this process so as to further improve purity. In this respect, the appellant's suggestion that the skilled person would in such a case repeat the treatment, not with fresh carbon, but with an already

used batch of carbon, is unrealistic, because the skilled person would anticipate that the column would be contaminated not just with the product but first and foremost with the impurities.

1.5.3 In summary, the skilled person starting from D11 and seeking to avoid the filtration step would turn to D13 and consider using a column containing phosphate-free granular activated carbon. Furthermore, the skilled person, aware of the potential issue of the presence of drug-degrading impurities in the resulting solution, would repeat as need be the same purification step without exercise of any inventive skills.

Accordingly, the main request does not meet the requirements of inventive step.

2. Auxiliary requests

2.1 In claim 1 of auxiliary request 2, the amount of drug-degrading agent in the resulting SAE-CD composition is more narrowly limited by an amended level in UV/vis absorption at 245-270 nm of less than ~~0.5~~ 0.25 A.U. for a tested concentration of ~~300~~ 500 mg per mL.

The appellant firstly argued that this stricter UV/vis absorption condition would establish a difference with the prior art D11. However, as for the main request, the appellant did not discharge their burden of proof in this respect as they did not present any evidence that the process of D11 exceeds the amended UV/vis absorption limit of claim 1.

The appellant further argued that the amended UV/vis absorption limit of claim 1 implied that the flow-through carbon treatment had to be repeated. However,

the Board's assessment of inventive step for the main request above already takes account of this repetition.

Claim 1 of auxiliary request 4 differs from claim 1 of the main requests in that it specifies that "the repeated treating comprises passing and recycling the partially purified aqueous solution through the mass of phosphate-free activated carbon two or more times, wherein each passing is with a different mass of activated carbon", and repeats that "the activated carbon is granular". As for auxiliary request 2, this limitation was already taken into account in the assessment of inventive step for the main request. The same conclusion thus applies.

Hence, neither auxiliary request 2 nor auxiliary request 4 meet the requirements of Article 56 EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

A. Vottner D. Boulois

Decision electronically authenticated