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Datasheet for the decision of 23 October 2025

Case Number: T 1965/23 - 3.3.07

Application Number: 12703898.2

Publication Number: 2667856

IPC: A61K9/19, A61K31/496, A61M5/00

Language of the proceedings: EN

Title of invention:
MEDICAL DEVICE CONTAINING A CAKE COMPOSITION COMPRISING ARIPIPRAZOLE AS AN ACTIVE INGREDIENT, AND A CAKE COMPOSITION COMPRISING ARIPIPRAZOLE AS AN ACTIVE INGREDIENT

Patent Proprietor:
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Opponents:
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Headword:
Aripiprazole cake composition/OTSUKA

Relevant legal provisions:
EPC Art. 83, 56
RPBA 2020 Art. 12(6)

Keyword:
Sufficiency of disclosure - (yes)
Inventive step - closest prior art - combination invention (yes)
Late-filed evidence - admitted (no)

Decisions cited:
T 0698/10, T 1450/16, T 0722/24

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Case Number: T 1965/23 - 3.3.07

D E C I S I O N
of Technical Board of Appeal 3.3.07
of 23 October 2025

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Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 7 December 2023 rejecting the opposition filed against European patent No. 2667856 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Usuelli
Members:	M. Steendijk
	S. Ruhwinkel

Summary of Facts and Submissions

I. European patent 2 667 856 ("the patent") was granted with twenty-two claims.

Claim 1 as granted defines:

"A medical device containing a separately prepared freeze-dried cake composition comprising aripiprazole as an active ingredient in a storage container whose inner wall is treated with silicone, wherein there is a space between the inner wall of the storage container and the cake composition."

Claim 11 as granted defines:

"A cake composition comprising aripiprazole as an active ingredient and having a strength of 5 to 100 N, wherein the cake composition has a cylindrical shape, and a side surface of the cylindrical cake composition is sloped, the angle of the slope being 0.1 to 10°."

Granted claim 18 defines a method for producing a medical device incorporating the features of the device as defined in claim 1. Granted claim 22 defines a method for producing a cake composition incorporating the features of the cake as defined in claim 11.

II. Four oppositions were filed against the grant of the patent on the grounds that its subject-matter lacked inventive step and that the claimed invention was not sufficiently disclosed.

The appeal was filed by opponents O1, O2 and O3 against the decision of the opposition division to reject the oppositions.

The opposition division cited *inter alia* the following documents:

D2: WO 2005/041937 A2
D3: JP H 0630974 A
D3a: Machine translation of JPH0630974A into English dated 5 November 2020
D11: WO 2005/042067 A2
D12: JP 4536825 B1
D12a: Machine translation of JP 4536825 B1 into English dated 24 March 2022
D18: US 5,788,670
D22: Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products, 3rd Edition, Informa Healthcare, 2010, chapters 15, 16 and 21
D28: https://www.otsuka.co.jp/en/company/newsreleases/2010/20 101006 1.html - OTSUKA ANNOUNCES PHASE 3 ARIPIPRAZOLE INTRAMUSCULAR (IM) DEPOT TRIAL INTERIM ANALYSIS REVEALS EFFICACY CRITERIA MET - October 6, 2010

The opposition division arrived at the following conclusions:

(a) Document D28 was not admitted for lack of relevance.

(b) The patent sufficiently disclosed the claimed invention.

(c) Document D2 represented the only reasonable starting point in the prior art.

The medical device of claim 1 as granted differed from the examples in document D2 in (i) the separately prepared cake composition, (ii) the space between the cake and the container inner wall, and (iii) the inner wall of the container being treated with silicone. The objective technical problem concerned the provision of a medical device for an injectable aripiprazole formulation, which exhibits improved use properties without particle agglomeration upon resuspension. No prior art suggested the silicone feature in combination with the cake features to achieve the evident benefit from the silicone treatment while preventing aripiprazole agglomeration.

The cake composition of claim 11 differed from the examples of document D2 in (i) the cylindrical shape, (ii) the slope of the side surface, and (iii) the strength of the cake. These features rendered the cake suitable to be prepared separately for subsequent use in siliconized devices wherein silicone-induced aripiprazole agglomeration is prevented. No prior art suggested the defined cake as a solution to the problem of preventing such agglomeration.

The same considerations applied with respect to claims 18 and 22 defining methods for producing the device of claim 1 and the cake composition of claim 11.

Accordingly, the patent as granted complied with the requirement of inventive step.

III. With the reply to the appeals, the patent proprietor relied on the claims as granted as its main request.

IV. In its communication pursuant to Article 15(1) RPBA, the Board expressed the following preliminary assessment:

- document D28 was not to be admitted into the appeal proceedings,

- the patent sufficiently disclosed the claimed invention,

- document D2, which relates to a freeze-dried preparation of aripiprazole represented the closest prior, not documents D11, D12 or D18, which related to medical devices without reference to aripiprazole,

- the objective technical problem in the decision under appeal concerned the provision of a medical device for an injectable aripiprazole formulation, which exhibits improved use properties without particle agglomeration upon resuspension and a cake formulation which is suitable for use in such a device

- the claimed subject-matter was not obvious as solution to the identified objective technical problem.

V. Oral proceedings were held on 23 October 2025.

VI. The arguments of the opponents relevant to the present decision are summarised as follows:

(a) Admittance of document D28

Document D28 represented evidence that intramuscular administration of aripiprazole for treatment of schizophrenia was part of the skilled person's common general knowledge. This information was *prima facie* relevant to the assessment of inventive step, in particular starting from document D12 as closest prior art.

(b) Sufficiency

The patent did not disclose how the strength of 5-100 N was to be measured, although it would be well known that different standard techniques provided different, and sometimes conflicting results.

The patent did not explain how a cake with a raised top-surface, as defined in dependent claims 5, 6 and 15, was to be obtained.

(c) Inventive step

The patent related to the technological field of medical devices for the administration of a pharmaceutical composition. Medical devices as described in documents D12, D11 and D18 differed from the subject-matter of granted claim 1 only in the feature of aripiprazole as the active ingredient. The freeze-dried aripiprazole composition described in document D2 differed from the subject-matter of claim 1 in a plurality of

structural features of the device, which were particularly prominent in the embodiment of the dual chamber syringe as defined in dependent claim 9. In line with the considerations in T 698/10 and T 1450/16, the devices known from documents D12, D11 and D18 therefore represented at least equally promising starting points in the prior art as the freeze-dried aripiprazole compositions of document D2.

The feature of a separately prepared freeze-dried cake composition, as defined in granted claim 1, did not require that the freeze-dried cake was prepared in a container separate from the storage container. According to paragraph [0046] and claim 2 of the patent such a separate preparation outside the storage container only represented a preferred embodiment. Moreover, the feature of the space between the inner wall of the storage container and the cake, as defined in claim 1, did not exclude the preparation of the cake composition by freeze-drying directly in the storage container, because the space was not further defined and could therefore include the space in the container above the cake, space formed by pores and cracks in the cake, and even the space occupied by silicone covering the inner wall of the container.

Document D2 already described a separately prepared freeze-dried cake composition comprising aripiprazole.

The difference of the subject-matter of granted claim 1 with the teaching of document D2 concerned the provision of the aripiprazole cake composition in a siliconised medical device.

The silicone-treated inner wall of the storage container of the device enhanced the smooth operation of the device, which was in particular evident in the case of dual chamber syringe as defined in dependent claim 9 of the patent. Insofar as the features of the separate preparation of the cake composition and the space relative to the inner wall of the container represented additional differentiating features, their effect of a reduced contact with the siliconised inner wall did not synergistically interact with the smooth operation of the device. It was therefore appropriate to separately formulate partial problems associated with these effects, namely the provision of aripiprazole in a device with smooth functionality and the provision of aripiprazole in a device in which the contact of the aripiprazole with the inner wall of the device is reduced.

The subject-matter of granted claim 1 was obvious in view of documents D12, D11 and D18, which already described the provision of separately prepared freeze-dried compositions in siliconised medical devices. In particular, document D12 described a dual chamber syringe in which a separately prepared freeze-dried composition was introduced for stable storage and ready to use upon reconstitution, which avoided the risk of contamination occurring when the reconstitution involves the transfer of an external liquid. Document D12 therefore provided the skilled person with a manifest motivation to include the freeze-dried aripiprazole composition of document D2 in such a dual chamber syringe and thereby arrive at

the subject-matter of dependent claim 9 and thus also independent claim 1 as granted.

The prevention of silicone-induced agglomeration of aripiprazole silicone was not an issue starting from document D2, because the preparation of the cake composition described in document D2 did not involve any contact with silicone.

Furthermore, it was not conclusively demonstrated that the agglomeration of aripiprazole could be prevented by the separate preparation of the cake composition and the presence of space between the cake and the container's inner wall as defined in granted claim 1, at least not for the whole scope of the claim. The experimental results presented in Tables 1 and 4, which the patent proprietor relied upon, did not permit the conclusion that the observed prevention of agglomeration originated from these features, because the experiments also differed in another critical aspect, namely whether the freeze-drying was performed in the presence or absence of silicone. The likely influence of this additional variable was supported by the absence of a clear correlation between the agglomeration after resuspension and the amount of silicone oil reported in Tables 1 and 4.

The skilled person, who was motivated to incorporate the freeze-dried aripiprazole from document D2 in a siliconised container, for instance as part of a dual chamber syringe, would in any case be concerned about any potential negative effects from a change in the formulation of the aripiprazole, including the presence of silicone. As evidenced by document D22, concerns

about negative effects of silicone, including particle formation, were part of the common general knowledge. Accordingly, the skilled person would opt for a device as described in document D12, which explicitly addresses the issue of storage stability and in which due to the external preparation of the freeze-dried composition, the contact with the siliconised inner wall of the container is reduced.

The difference between the subject-matter of granted claim 11 and the teaching of document D2 concerned the defined shape of the cake composition. The strength of the composition did not constitute any difference. Although document D2 did not explicitly address the strength of the composition, the example for the preparation of freeze-dried compositions described in document D2 essentially corresponded to the preparation of the examples in the patent, wherein the freeze-drying of liquid compositions comprising about 10% solid material resulted in a strength above 5 N.

Whilst the shape of the defined cake composition comprising aripiprazole and possibly its strength could facilitate the integral removal of the cake from the container in which it was prepared, these features were unrelated to the prevention of agglomeration of aripiprazole. In fact, claim 11 comprised any cake with the defined shape and strength, irrespective of whether the cake was to be removed from the container in which it had been prepared or not. The objective technical problem underlying the subject-matter of claim 11 therefore concerned the mere provision of an alternative cake composition.

The cake composition of granted claim 11 was in any case obvious as a solution to the problem of providing an easily removable cake composition comprising aripiprazole in view of document D3, which already described the conical shape for a freeze-dried composition to facilitate its integral removal from the container in which it had been separately prepared and which implicitly required a suitable strength to allow such handling. Moreover, the provision of a separately prepared cake composition was motivated by the teaching of document D12.

VII. The arguments of the patent proprietor relevant to the present decision are summarised as follows:

(a) Admittance of document D28

Document D28 did not represent common general knowledge and lacked *prima facie* relevance.

(b) Sufficiency

The patent provided sufficient instructions on how to prepare cake compositions with a strength within the defined range, how to measure such strength and how to obtain a cake composition with a raised top-surface.

(c) Inventive step

The claimed invention was aimed at the formulation of aripiprazole. The closest prior art was represented by document D2, which related to the same purpose. In contrast, the cited prior art

relating to medical devices in general, such as document D12, made no reference to the purpose of the claimed invention. The mere number of corresponding features was not decisive.

The skilled person would understand the feature of a separately prepared freeze-dried cake composition as defined in granted claim 1 to require that it had been prepared outside the storage container. This interpretation was confirmed by paragraph [0046] of the patent and was not challenged by the definition of a preferred embodiment in which the composition is freeze-dried in a container separate from the storage container. The feature of the space between the inner wall of the storage container and the cake, as defined in claim 1, clearly excluded a form-locking placement of the cake in the storage container and did not relate to cracks and pores in the cake or a silicone layer on the inner wall of the container.

Document D2 described the preparation of a freeze-dried composition comprising aripiprazole inside the vials in which the composition was stored.

The differences between the subject-matter of granted claim 1 and the teaching of document D2 concerned the separate preparation of the cake composition, the space between the cake composition and the inner wall of the storage container, and the silicone treatment of the inner wall of the storage container.

It was evident to the skilled person that the silicone treatment of the inner wall of the storage container improved the functioning of the defined

device. The experimental results reported in Table 1 and Table 4 demonstrated that the separate preparation and the space between the cake composition and the siliconised inner wall prevented agglomeration of the aripiprazole upon reconstitution, otherwise due to silicone contamination of the cake composition. The results reported in Table 1 and Table 4 indicated a fair correlation between the observed agglomeration and the amount of silicone oil in the composition after resuspension. The only outlier concerned example 2-1, in which the relatively high amount of silicone measured in the suspension likely resulted from contamination during the resuspension and not from contamination of the cake composition during storage. The argument that the demonstrated prevention of agglomeration was due to the absence of silicone in the container in which the compositions were freeze-dried, rather than the reduced contamination with silicone from the inner wall of the container during storage, lacked substantiation.

The technical effects of the distinguishing features were interrelated, because the silicone-treated inner wall of the storage container of the device improved the functioning of the device and the separate preparation and the space between the cake composition and the inner wall avoided silicone-induced agglomeration of the aripiprazole.

The objective technical problem was therefore the provision of a medical device for an injectable aripiprazole formulation, which exhibits improved use properties without undesired particle agglomeration upon resuspension.

The prior art provided no suggestion towards the subject-matter of granted claim 1 as a solution to this objective technical problem. Document D22 merely referred to the possible particle formation of proteins due to the presence of silicone and provided no suggestion that the presence of silicone would induce the agglomeration of aripiprazole. Faced with the objective technical problem, the skilled person had no motivation to apply the teaching of documents D12 or D11 to the formulation of aripiprazole, because these documents were not concerned with the issue of agglomeration of the active ingredient due to silicone contamination from the storage container. In further developing the formulation of document D2, the skilled person was in view of the many conceivable options also not confronted with a one-way-street situation leading to the claimed invention. The subject-matter of granted claim 1 therefore involved an inventive step.

The difference between the subject-matter of granted claim 11 and the teaching of document D2 concerned the defined shape of the cake composition and the strength of the composition. The strength of the exemplified freeze-dried composition described in document D2 could not be adequately established on the basis of the similarity of its preparation as compared to the examples in the patent due to the critical influence of the concentration of the suspension before freeze-drying, which differed between the relevant examples.

The defined shape and strength of the cake composition allowed its easy removal and separate handling. These features therefore rendered the composition particularly suitable for use in the device of granted claim 1. The objective technical problem underlying the subject-matter of granted claim 11 was therefore also concerned with the prevention of undesired particle agglomeration upon its resuspension after storage in a siliconised storage container.

The prior art provided no suggestion towards the subject-matter of claim 11 as a solution to this objective technical problem. Document D3 described the preparation of removable freeze-dried compositions in a mould for their subsequent transfer into infusion bags. The skilled person had no reason to apply the teaching of document D3 to aripiprazole, which was administered orally or by intramuscular depot injection. Document D12 related to the preparation of a freeze-dried composition in a sleeve for transfer to a medical device, which did not result in a sloped side surface and did not require the strength for separate handling.

VIII. The appellants-opponents requested that the decision be set aside and the patent be revoked in its entirety.

Insofar as relevant to the decision, they further requested that document D28 be admitted as evidence of common general knowledge.

IX. The respondent-patent proprietor requested that the appeals be dismissed.

Insofar as relevant to the decision, the patent proprietor further requested that document D28 not be admitted.

Reasons for the Decision

1. Admittance document D28

Document D28, which represents a press-release from the patent proprietor concerning a phase 3 clinical trial with aripiprazole intramuscular depot injections, was filed by O1 with the letter of 18 September 2023 in response to the opposition division's communication under Rule 116(1) EPC. The opposition division considered that it was not evident that document D28 represented common general knowledge, that document D28 presented no new information beyond what was already on file, and that its filing was not responsive to the opposition division's preliminary opinion. The opposition division therefore decided not to admit document D28.

In its communication under Article 15(1) RPBA, the Board indicated that it seemed questionable that document D28 was representative of the common general knowledge and that the information in document D28 relied upon by O1 was otherwise already on file in document D2. The Board therefore expressed the preliminary opinion that the opposition division's decision not to admit document D28 did not suffer from an error in the use of discretion and that the circumstances of the appeal case did not justify the admittance of document D28.

No substantive arguments were submitted by the opponents in response to the Board's preliminary opinion.

Accordingly, the Board confirmed its preliminary opinion and decided not to admit document D28 under Article 12(6), first sentence, RPBA.

2. Sufficiency

In its communication under Article 15(1) RPBA, the Board indicated that the patent described in paragraph [0081] and examples 5 and 8 how to prepare cake compositions with a variety of strengths within the defined range depending on the solid content of the freeze-dried suspension. The patent further described in paragraph [0086] how to measure such strength, and in example 1 how a cake composition comprising a raised top surface can be obtained using a polyethylene container. In the absence of evidence supporting the opponents' objections, the Board therefore expressed the preliminary opinion that the patent sufficiently disclosed the claimed invention.

No substantive arguments were submitted by the opponents in response to the Board's preliminary opinion.

The Board therefore confirmed its preliminary opinion that the patent as granted sufficiently disclosed the claimed invention as required under Article 83 EPC.

3. Inventive step

3.1 Starting point in the prior art

3.1.1 The patent addresses the specific issue of the agglomeration of aripiprazole following resuspension when it is provided as a cake composition in a storage container of a medical device, such as a syringe, of which the inner wall is treated with silicone (see the patent, paragraphs [0011]-[0013]). The patent teaches in this context that by reducing the contact of the cake composition comprising aripiprazole with the silicone this agglomeration can be suppressed (see the patent, paragraph [0014]). The patent presents experimental results in support of this teaching (see examples 2-1 to 2-9 in Table 1 and comparative examples 1-1 to 1-9 in Table 4).

In this context, claim 1 of the patent defines a medical device containing a separately prepared freeze-dried cake composition comprising aripiprazole in a storage container with a silicone-treated inner wall, wherein a space is left between the cake and the inner wall. Claim 11 further defines a cake composition comprising aripiprazole, specifying features of its shape and strength.

The aim of the claimed invention thus concerns the formulation of a composition comprising aripiprazole as an active ingredient. The problem it addresses relates to the prevention of agglomeration of aripiprazole following reconstitution from a freeze-dried composition stored in silicone-treated container.

3.1.2 According to the established jurisprudence (see Case Law of the Boards of Appeal of the EPO, 11th edition,

2025, I.D.3.4) a central consideration in selecting the closest prior art is that it must be directed to the same purpose or effect as the claimed invention; otherwise, it cannot lead the skilled person in an obvious way to the claimed invention. The central role of the purpose or effect of the claimed invention is confirmed in T 698/10, cited by the opponents, which explicitly states that as a first criterion, the closest prior art should be related to the claimed invention, in the sense that it should disclose subject-matter conceived for the same purpose or aiming at the same objective (see T 698/10, point 3 of the Reasons). In T 1450/16, also cited by the opponents, the Board considered that the selection of the closest prior art is to be made on the basis of the established criteria, in order to avoid any hindsight analysis (see T1450/16, Headnote). As explained above, the established central criterion concerns the purpose or effect of the claimed invention.

The board notes in this context that the problem-solution approach implies that if an inventive step is convincingly denied in view of a realistic starting point in the prior art, an argument that the claimed subject-matter nevertheless involves an inventive step in view of a supposedly closer prior art is generally unconvincing, since in such a case the supposedly closest prior art appears to be less promising. However, if an inventive step can be acknowledged starting from a particular prior art that is convincingly identified as the most promising starting point and therefore indeed constitutes the closest prior art, the attempt to deny an inventive step starting from a less promising starting point must fail (see Case Law of the Boards of Appeal of the European Patent Office, supra, I.D.3.7.1-3.7.2). The concept of

the closest prior art in the problem solution approach not only obviates the need to address repetitive lines of argument, it also allows for the due appreciation of specific effects in relation to the prior art that may be associated with the distinguishing features (see T 722/24, point 5.1.2 of the Reasons).

3.1.3 Document D2 describes the preparation of a formulation comprising aripiprazole by freeze-drying a suspension in a vial (see D2, example 1) and thus addresses a similar purpose as the patent, namely the formulation of a composition comprising aripiprazole as active ingredient. Document D2 thereby provides a reasonable starting point for the development of a formulation of a freeze-dried composition comprising aripiprazole as an active ingredient as defined in the patent.

As pointed out in the decision under appeal, documents D12, D11 and D18 describe silicone-treated medical devices comprising freeze-dried formulations without mention of aripiprazole or problems resulting from the presence of silicone. Documents D12, D11 and D18 therefore do not address a similar purpose or effect as the patent. Arriving at the development of a freeze-dried composition comprising aripiprazole in a silicone-treated container of a medical device as disclosed in the patent starting from these documents would require the clueless choice of aripiprazole from all possible candidates of active ingredients, which the Board does not consider a reasonable proposition. The Board therefore considers that documents D12, D11 and D18 do not represent reasonable alternative starting points in the assessment of inventive step, irrespective of the number of other features shared with the claimed subject-matter.

3.2 Objective technical problem - granted claim 1

3.2.1 The Board agrees with the finding in the decision under appeal that the medical device defined in claim 1 as granted differs from the teaching presented in document D2 in that (i) the cake composition is prepared separately from the storage container, (ii) there is a space between the cake and the inner wall of the container and, (iii) the inner wall is treated with silicone.

In this context, the Board considers that the only technically reasonable interpretation of the feature concerning the space between the cake composition and the inner wall of the container, when read in conjunction with the definition of separate preparation, is that the space results from placing the cake composition into a storage container with internal dimensions larger than those of the cake itself. This space is therefore located between the cake and the side wall of the container and constitutes a void that is neither filled with silicone nor formed by cracks or pores within the cake. Accordingly, granted claim 1 excludes any form-locking placement of the cake within the storage container. This interpretation corresponds with the explanation provided in the patent (see paragraph [0046]), which states that the cake composition is prepared separately and subsequently transferred into the storage container. The embodiment of dependent claim 2 as granted, which is identified as preferred in paragraph [0046] of the patent, explicitly involves preparing the cake composition in a container separate from the storage container. However, this does not imply that claim 1 encompasses a form of separate preparation carried out within the storage container itself as a non-preferred embodiment.

The Board therefore does not follow the opponents' argument that document D2 already discloses the feature of the separate preparation of a freeze-dried cake as defined in granted claim 1, because according to the examples of document D2 the freeze-dried composition is prepared in the vials in which the composition is stored.

3.2.2 The silicone treatment of the inner wall of the storage container evidently enhances the functionality of the device, particularly when the device is a syringe. This was undisputed.

3.2.3 As noted in section 3.1.1 above, the patent addresses the issue of the undesired agglomeration of aripiprazole following resuspension of freeze-dried aripiprazole when stored in a container of a medical device with a silicone-treated inner wall. The patent presents in Table 1 and Table 4 (reproduced below) experimental results which indicate that after one month of storage of freeze-dried aripiprazole in a silicone-treated syringe, agglomeration of aripiprazole particles is observed upon resuspension when the freeze-drying is performed within the syringe (see paragraphs [0135]-[0138], comparative examples 1-1 to 1-9 in Table 4), whereas no such agglomeration is observed when the freeze-drying is carried out externally and the resulting cake composition is subsequently transferred into the syringe for storage (see paragraphs [0107]-[0113], examples 2-1 to 2-9 in Table 1).

Table 1

Example No.	Mean particle size of aripiprazole in the suspension before freeze-drying (μm)	Concentration of silicone oil in the emulsion (% by mass)	Amount of silicone oil on the syringe (μg/100 mm²)	One-month storage at room temperature		
				Amount of silicone oil in the cake composition after resuspension (μg/100 mg of the active ingredient)	Mean particle size of aripiprazole (μm)	
					Without Ultrasonic treatment	With ultrasonic treatment
2-1	2.1	35	75	22	2.1	2.1
2-2		20	45	6	2.1	2.1
2-3		15	36	7	2.1	2.0
2-4		10	24	4	2.1	2.0
2-5		7	14	4	2.1	2.1
2-6		5	11	3	2.1	2.0
2-7		2	3	5	2.0	2.0
2-8		1	2	4	2.0	2.0
2-9		0.5	1	5	2.1	2.1
Reference Example		0	0	2	2.0	2.1

Table 4

Comparative Example No.	Mean particle size of aripiprazole in the suspension before drying (μm)	Concentration of silicone oil in the emulsion (% by mass)	Amount of silicone oil on the syringe (μg/100mm²)	One-month storage at room temperature		
				Amount of silicone oil	Mean particle size of aripiprazole (μm)	
				in the cake composition after resuspension of the active ingredient)	Without ultrasonic treatment	With ultrasonic treatment
1-1	2.2	35	75	49	3.5	25
1-2		20	45	41	3.1	23
1-3		15	36	49	3.1	2.4
1-4		**10**	24	38	3.1	24
1-5		7	14	27	2.9	2.4
1-6		5	11	24	2.8	23
1-7		2	3	26	2.7	2.2
1-8		1	2	16	2.6	23
1-9		0.5	1	19	2.5	23
Reference Example		0	0	14	2.3	2.2

The examples 2-1 to 2-9, for which the results in Table 1 indicate that agglomeration upon resuspension after storage is prevented, reflect the distinguishing features of claim 1, namely the silicone-treated inner wall of the storage container and the separately prepared freeze-dried cake composition which leaves a

space with the silicone-treated inner wall of the storage container.

The opponents objected that the presented results did not conclusively demonstrate that the observed prevention of agglomeration originated from the distinguishing features of granted claim 1. Instead, they suggested that the absence of silicone contamination during freeze-drying was responsible, which is not a feature of claim 1 as granted. They supported their objection by reference to the absence of a clear correlation between the amount of silicone present in the composition and the extent of agglomeration reported in Table 1 and Table 4.

The Board rejects this objection as unsubstantiated. Contrary to the opponents' argument, the results reported in Table 1 and Table 4 show a fair correlation between the observed agglomeration upon resuspension after storage and the amount of silicone oil in the composition after resuspension. The only outlier is represented by example 2-1, for which no agglomeration was observed in spite of a relatively high amount of silicone in the resuspended composition. However, this example involves the storage of a separately prepared cake composition in a syringe treated with the highest load of silicone, wherein the amount of silicone in the resuspended composition is plausibly explained by contamination during the resuspension, rather than by contamination during the storage of the cake.

It is therefore reasonable to conclude from the results in Table 1 and Table 4 that the silicone contamination of the freeze-dried cake during storage promotes the agglomeration of aripiprazole upon resuspension and that this contamination can be avoided by providing a

separately prepared cake composition which limits the contact with the silicone as defined in claim 1 as granted. Even if silicone contamination during the separate preparation of the cake composition is not prevented, the feature of the separate preparation of the cake composition leaving a space with the silicone-treated inner wall of the storage container should in any case prevent the further contamination with silicone during storage and thereby reduce the tendency of agglomeration.

3.2.4 As correctly noted in the decision under appeal, the technical effects of the distinguishing features are interrelated. The silicone enhances the functionality of the claimed device, while the separate preparation of the cake composition and the presence of a space between the cake and the silicone-treated inner wall of the storage container prevents agglomeration of aripiprazole upon resuspension after storage. This agglomeration would otherwise occur due to the contamination of the cake with silicone.

In accordance with the established jurisprudence (see Case Law of the Boards of Appeal of the European Patent Office, *supra*, I.D.9.3) the mentioned functional relationship between the identified distinguishing features justifies the formulation of the combined objective technical problem. The Board does not recognize that in this context some further synergy between the discussed effects of the distinguishing features is required, as contended by the opponents.

In line with the decision under appeal, the Board therefore formulates the objective technical problem underlying the subject-matter of granted claim 1 as the provision of a medical device for an injectable

aripiprazole formulation, which exhibits improved use properties without particle agglomeration upon resuspension.

3.3 Objective technical problem - granted claim 11

3.3.1 The Board agrees with the finding in the decision under appeal that the cake composition defined in claim 11 as granted differs from the teaching in document D2 in the defined shape, cylindrical with the sloped side surface, in combination with the defined strength.

The opponents argued that the strength of the composition was not a distinguishing feature, because the exemplified preparation of freeze-dried compositions in document D2 essentially corresponded to the preparation of examples of freeze-dried cakes with sufficient strength in the patent. In their view, document D2 thus implicitly disclosed the strength required by granted claim 11. However, the patent demonstrates that the strength of a freeze-dried cake depends on the concentration of the aripiprazole in the composition before freeze-drying (see paragraphs [0125]-[0126], Table 2 and paragraphs [0133]-[0134], Table 3). The patent reports in this context a strength of 6.90 N for a cake prepared with similar components as the examples of document D2, but comprising 10.5 % by mass of aripiprazole (see paragraph [0125], Table 2) instead of the 100/1040=9.6% by mass of the examples of document D2 (see D2, pages 18-21, Examples 1-2). It remains therefore speculative whether the examples in document D2 would reach a strength of 5-100 N as defined in claim 11 of the patent. The opponents' argument is therefore not convincing.

3.3.2 It was not in dispute that the shape and strength of the defined cake composition facilitates the integral removal and handling of the cake from the container in which it is prepared.

The opponents denied that the shape, strength, and removability of the defined cake composition were inherently linked to the prevention of aripiprazole agglomeration in the presence of silicone and argued that claim 11 encompassed any cake exhibiting the specified shape and strength, regardless of whether it was intended to be removed from the container in which it was prepared.

However, as the decision under appeal correctly explained, the facilitated removability of the cake, which results from its distinguishing features, renders it especially suitable for use in a silicone-treated device, as described in claim 1. In this device, the use of a separately prepared cake allows for the prevention of aripiprazole agglomeration, which would otherwise occur due to contamination of the cake with silicone.

3.3.3 The Board therefore considers that the subject-matter of granted claim 11 addresses essentially the same objective technical problem as formulated for the subject-matter of granted claim 1 by providing a cake formulation particularly suitable for use in a medical device for an injectable aripiprazole formulation, which exhibits improved use properties without particle agglomeration upon resuspension.

3.4 Assessment of the solution

3.4.1 Faced with the identified objective technical problem, the skilled person would not, based on the available prior art, have arrived in any obvious manner at the subject matter of independent claims 1 and 11 as granted as a solution. As set out in sections 3.4.2-3.4.5 below, it had not been recognized in the prior art cited by the opponents that contamination by silicone during the storage of a freeze-dried aripiprazole cake leads to undesired agglomeration upon its resuspension. Furthermore, the prior art provided no suggestion that problems arising from silicone contamination of freeze-dried cakes of active ingredients, whether aripiprazole or other agents, could be resolved by incorporating a separately prepared freeze-dried cake into a medical device in such a way that a space is left between the cake and the silicone-treated inner wall of the device's storage container.

3.4.2 Document D2 is entirely silent as to the identified problem and its solution.

3.4.3 Document D22 recognises that silicone in injectable formulations may lead to a variety of problems and mentions in this context the possible particle generation by siliconised stoppers, when silicone oil particles act as a nucleus to attract other materials such as proteins, for instance TNF (see D22, page 409). Document D22 further instructs that, when silicone compatibility is an issue, the formulation or the process needs to be optimised (see D22, pages 499-500).

However, document D22 neither mentions any specific agglomeration problem with aripiprazole caused by

silicone contamination, nor provides any suggestion toward the solution claimed in the patent.

3.4.4 Document D12 describes the separate preparation of a freeze-dried composition for an injectable formulation in a sleeve, which allows its transfer into a silicone-treated dual chamber syringe (see, translation D12a, for instance paragraphs [0012] and [0029]). It was undisputed that the teaching of document D12 differs from the subject matter of granted claim 1 solely in that it does not specify any particular active ingredient, and therefore does not disclose a medical device comprising aripiprazole as the active ingredient.

Document D11 also describes the separate preparation of a freeze-dried composition for an injectable formulation for transfer to the container of a dual chamber medical device, of which the plunger and sealing members may be lubricated with silicone (see D11, paragraphs [0005], [0083], [0038] and [0044]).

Document D18 describes a further pre-fillable dual chamber syringe, wherein a freeze-dried composition may be freeze-dried in one of the separate containers of the device, which may be coated with silicone (see D18, column 8, lines 59-67 and claim 8).

However, none of these documents mention aripiprazole or address issues arising from the contamination of the freeze-dried composition of any active ingredient by silicone during storage in the device. The skilled person had therefore no reason to adopt the teaching of any of these documents, including document D12, to solve the identified objective technical problem

underlying the subject-matter of independent claims 1 and 11.

3.4.5 Document D3 describes a container for preparing a freeze-dried drug, such as an antibiotic or a protein, from which the freeze-dried composition can be easily removed to conveniently fill a container which is itself unsuitable for freeze-drying, such as a flexible container made of plastic, for instance an infusion bag. The container for freeze-drying may have a cylindrical shape having a cross section which increases towards its upper end (see translation D3a, paragraphs [0002], [0003], [0012] and figure 9).

Although it is clear that the separately freeze-dried composition that is removed from the container in accordance with document D3 assumes the shape of the cake as defined in claim 11 and must possess at least sufficient strength to be transferred, for example, to an infusion bag, document D3 does not identify any problem regarding the agglomeration of an active ingredient upon resuspension, nor does it provide any suggestion toward the solution claimed in the patent. The skilled person had therefore no reason to adopt the teaching of document D3 to solve the identified objective technical problem underlying the subject-matter of independent claims 1 and 11.

3.4.6 In view of the evident advantages of pre-filled medical devices for injectable formulations, such as dual chamber syringes, the skilled person may have considered the provision of a freeze-dried composition as described in document D2 in such a device. However, it was undisputed that the prior art offers in this respect a variety of conceivable options, as evidenced, for instance, by the different configurations described

in the above mentioned documents D12, D11 and D18. The opponents did, however, not present any compelling reason why the skilled person would, in this context, choose the syringe disclosed in document D12. In the absence of a compelling motivation, the opponents' argument that, regardless of the issue of agglomeration of aripiprazole upon resuspension, the skilled person would in any case combine the teachings of documents D2 and D12 to arrive at the subject matter of independent claims 1 and 11, appears driven by impermissible hindsight and contradicts the established problem-solution approach.

The opponents further argued that the skilled person would, in any case, apply the teaching of document D3 to the freeze-dried composition described in document D2. However, in the absence of any compelling reason to do so, and having regard to the identified objective technical problem, this argument appears also driven by impermissible hindsight and is therefore not persuasive.

3.5 Granted claims 18 and 22 define methods for producing a medical device and a cake composition incorporating the features of the device as defined in claim 1 and claim 11. The opponents did not raise any separate objection of lack of inventive step against claims 18 and 22. The considerations as set out for claims 1 and 11 therefore equally apply with respect to claims 18 and 22

3.6 Accordingly, the Board concludes that the patent as granted complies with the requirement of inventive step as define in Article 56 EPC.

Order

For these reasons it is decided that:

The appeals are dismissed.

The Registrar: The Chairman:

A. Vottner A. Usuelli

Decision electronically authenticated