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Datasheet for the decision of 21 October 2022

Case Number: T 1318/18 - 3.3.08

Application Number: 11788050.0

Publication Number: 2652123

IPC: C12N5/00, A61K9/20

Language of the proceedings: EN

Title of invention:
DRY GRANULATED CELL CULTURE MEDIA

Patent Proprietor:
Merck Patent GmbH

Opponent:
Hüttermann, Aloys

Headword:
Dry granulated cell culture media/MERCK

Relevant legal provisions:
EPC Art. 54, 56, 100(a), 100(b)
RPBA Art. 12(4)

Keyword:
"Main Request - requirements of the EPC met (yes)"

Decisions cited:
T 2050/07

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 1318/18 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 21 October 2022

Appellant: (Opponent)	Hüttermann, Aloys Michalski Hüttermann & Partner Speditionstrasse 21 40221 Düsseldorf (DE)
Representative:	Wichmann, Hendrik Wuesthoff & Wuesthoff Patentanwälte PartG mbB Schweigerstraße 2 81541 München (DE)
Respondent: (Patent Proprietor)	Merck Patent GmbH Frankfurter Strasse 250 64293 Darmstadt (DE)
Representative:	Schmid-Großmann, Uschi Mier, Regina Merck Patent GmbH 64271 Darmstadt (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 28 March 2018 rejecting the opposition filed against European patent No. 2652123 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	B. Stolz
Members:	D. Pilat
	D. Rogers

Summary of Facts and Submissions

I. European patent No. 2 652 123 is based on European patent application No. 11 788 050.0, (published as WO 2012/079679 on the 21 June 2012). The patent, entitled "DRY GRANULATED CELL CULTURE MEDIA", was opposed on the grounds of Article 100(a) in conjunction with Articles 54 and 56 EPC, and of Article 100(b) EPC. An opposition division considered the patent as granted to fulfill the requirements of the EPC.

II. The opponent (appellant) lodged an appeal against the decision of the opposition division and submitted new documents E44 to E46.

III. The patent proprietor (respondent) replied to appellant's statement of grounds of appeal and submitted five auxiliary requests.

IV. Appellant submitted further observations in reply to the proprietor's submissions.

V. The appellant without making any substantive submissions, announced its intention not to attend oral proceedings.

VI. The board summoned the parties to oral proceedings and, in a communication sent in preparation of the oral proceedings, expressed its provisional opinion, inter alia on issues concerning Articles 83, 54 and 56 EPC.

VII. With a letter dated 22 July 2022, the respondent, without making any substantive submissions, announced its intention not to attend the oral proceedings in

view of the preliminary opinion expressed in the board's communication.

VIII. Oral proceedings were cancelled.

IX. Claim 1 of the main request (granted claims) reads as follows:

"1. The use of a dry granulated cell culture medium which does not comprise peptones or tryptones preparable by
a) providing a cell culture medium comprising one or more saccharide components, one or more amino acids, one or more vitamins, one or more salts, one or more buffer components, one or more co-factors and one or more nucleic acid components, in form of a mixed powder of the medium components, whereby the medium does not comprise peptones or tryptones
b) compacting said mixed powder in a roll press,

characterized in that step b) is performed by

b1) compacting said mixed powder in a roll press
b2) reintroducing all parts of the compacted cell culture medium obtained in step b1) which have a particle size of smaller than 0.5 mm into the cell culture medium in form of a mixed powder of the medium components to be filled in the roll press

for culturing cells by:

a) dissolving the dry granulated cell culture medium which does not comprise peptones or tryptones in a solvent to form a liquid cell culture medium
b) contacting said liquid cell culture medium with said cells to be cultured".

Dependent claims 2 to 8 define specific embodiments of claim 1.

X. The following documents are referred to in this decision:

E1: WO 02/36735 A2, published on 10 May 2002;
E2: US 2008/0254119 A1, published on 16 October 2008;
E3: R. Fike *et al.* Cytotechnology, vol.36, pages 33-39, (2001);
E7: Wibowo C. and Ng K.M. AIChE Journal, vol.45 (8), pages 1629-1648 (1999);
E8: Miller, R. W., Roller Compaction technology, pages 159-190; in Handbook of Pharmaceutical Granulation Technology, 2nd ed. 2005; (Parikh, D.M., ed.);
E10: P. Kleinebudde, European Journal of Pharmaceutics and Biopharmaceutics vol.58, pages 317-326, (2004);
E22: DE 2 220 065, published on 1973;
E29: Letter of Applicant/Proprietor dated 15 August 2014;
E32: Media formulation of 10x concentrated "Medium 199" retrieved from the internet in September 2017;
E33: Sigma Aldrich data sheet for MCDB 131 Medium, 2007;
E34: Sigma Aldrich data sheet for MCDB 153 Medium, 2007;
E36: Handbuch der Mechanischen I Verfahrenstechnik, H. Schubert, ed., Band 1, ISBN 3-527-30577-7, pages 212-269, 434-437, 460-481, and 492-499 (2003);

E37: Handbuch der Agglomerationstechnik, G. Heinze, ed., ISBN 3-527-29788-X, pages 28-35, 47-48, 57-58, 119-129, and 134-146, (2000);

E38: German Wikipedia entry "Hefeextrakt", retrieved from the internet in September 2017;

E39: DSMZ, recipe for Glucose Yeast Extract Medium, (2010);

E40: Remington, The Science and Practice of Pharmacy, 21st edition, ISBN 0-7817-4673-6, pages 891-892 (2006);

E41: A. Salazar *et al*. Powder Technology, vol.301, pages 110-117,(2016);

E42: Attachment 1 of E30;

E46: The internet archive WayBackMachine, website of the DSMZ dated 18 March 2010;

E47: Composition of a cell culture medium according to claim 1;

E48: Result of a compaction of a composition of a cell culture medium according to claim 1.

XI. The submissions made by the appellant as far as relevant to this decision were essentially as follows:

Claim interpretation

Claim 1 used the expression "dry granulated cell culture medium". The "dry granulated cell culture medium" could be interpreted either as a cell culture medium which had been subjected to dry granulation or as a dry cell culture medium in granulated form. The latter medium was repeatedly compared to a dry powdered cell culture medium (see paragraphs [0012], [0014] (prior art section); [0016] (object of the invention); [0017] (solution claimed)). The dry cell culture medium in granulated form might be prepared by wet granulation or dry granulation. The dry cell culture medium

obtained by dry granulation, preparable by applying a step of compacting said mixed powder in a roll press, could not be distinguished from a dry cell culture medium obtained by wet granulation.

Although the patent mentioned that dry granulation conditions were allegedly milder than wet granulation conditions and allowed for the direct and easy processing of media comprising heat- and/or oxidation sensitive substances like vitamins, glucose, thiamine, iron salts or components comprising disulfide bonds (see paragraphs [0014] to [0016] and [0076]), no experimental evidence demonstrated that this roller compacting step preserved these components from alteration or destruction. The advantage conferred by the compacting of said mixed powder in a roll press over wet granulation (document E1) and/or tableting (document E22) was not credible based on the content of the patent application.

The step of compacting said mixed powder in a roll press in the product by process definition of claim 1 could not confer any property to the dry cell culture medium in granulated form and as such could not confer a technical character to the dry granulated cell culture medium. The breaking edges of the granules of the medium were due to the way it was prepared and had not been shown to have an effect on the culturing of the cells by a) dissolving the dry granulated cell culture medium and b) contacting said liquid cell culture medium with said cells to be cultured.

The reintroduction of all parts of the compacted cell culture medium obtained in step b1) which have a particle size of smaller than 0.5 mm into the cell culture medium in the form of a mixed powder of the

medium components to be filled in the roll press might distinguish the method of preparing dry granulated media from dry powdered media. However, this step was not shown to confer any technical effect to dry cell culture media apart from an increase in the cost-efficiency of the process.

Dependent claim 5 clarified that the method of claim 1 could comprise a further step c), following step bl) and step b2), in which the material obtained from compacting said mixed powder in a roll press is further processed in a sieve mill. The process of preparing the dry granulated cell culture medium could therefore involve additional steps, which did not allow a final particle size for the dry granulated cell culture medium to be fixed.

Sufficiency of disclosure

The only example of the patent did not fall under the ambit of claim 1. The supplementary evidence submitted by the respondent to address the objection raised under Article 83 EPC during examination was provided with insufficient information to allow the skilled person to reliably and validly reproduce the tests made.
There was no indication of the process parameters, such as the milling degree, size of the rolls, roller speed and press force. The cell culture medium composition used in the supplementary experiments was not defined and thus not reproducible. It was furthermore unclear how the hydrates in salts, the percentage of the saccharides in the medium had to be calculated. It was unclear why the components in media D and E added up to a percentage value by weight above and below 100% going beyond a rounding error. The indication that *nucleic acid compounds are ">0"* was obscure. Finally, the

presence of a cofactor in the cell culture medium was questioned.

Document E41 provided no evidence that the process defined in claim 1 was sufficient to prepare the dry-granulated cell culture medium used in claim 1. Besides, it was unknown whether the media used in document E41 contained saccharides and at least one cofactor.

The type and content of saccharide was essential as a binding agent for the invention to be carried out (see documents E8, page 160, middle of the page; E37, page 30, and E40, paragraph bridging pages 891 and 892). For this reason and based on documents E37 and E40, the technical effect could not be plausibly achieved over the whole scope of claim 1 and the invention therefore not carried out without undue burden across the entire claimed scope.

Document E48 was a representation of a compacted cell culture medium whose compaction was carried out according to the specifications of the patent. Document E47 defined the composition of the cell culture medium according to claim 1 that was compacted and represented in document E48. However, there was no indication of what "according to the specifications of the patent" had to mean. Under these circumstances, it was doubtful that the compaction shown in document E48 was reproducible.

Since the patent failed to provide at least one example of and sufficient information on how the invention could be put into practice over the entire breadth of the claims, there was only a weak presumption that the invention was sufficiently disclosed.

Under these circumstances appellant could discharge his burden of proof by plausibly arguing that the skilled person would not be able to put the invention into practice over the entire breadth of the claim using common general knowledge (see decision T 63/06, reasons points 3.1.1-3.2.2).

Novelty

Neither the components of the medium nor the steps of preparing said medium or reintroducing particles of small size into the mixed powder could establish novelty.

Document E1 disclosed a method for producing a dry cell culture medium comprising the salt and buffering agent sodium bicarbonate (see page 51, line 12; page 53, lines 14 to 17; and page 57, lines 18 to 21 of document E1). The cell culture medium was intended for culturing mammalian cells such as CHO cells, COS cells, VERO cells, BHK cells, AE-1 cells, SP2/0 cells, L5.1 cells, hybridomas cells or human cells (see page 10, lines 16 to 18). Typical media components were amino acids, salts, vitamins, sugars (i.e. saccharides), nucleic acids and sodium bicarbonate (see page 17, lines 18 to 19, and page 15, lines 16 to 24). Medium 199, MCDB 131 and MCDB 153 were without tryptone and peptone as shown in documents E32, E33 and E34 respectively (see page 21, lines 10 to 26). The combined use of a spray-drying apparatus and a fluid bed apparatus integrated within the drying chamber was used for the production of powders from heat-sensitive formulations of nutritive media. A spray-dried and agglomerated powdered nutritive medium was obtained (i.e. granulated cell culture media)(see Examples 5 and 6 and page 35, line 26 to page 36, line 3).

The step b2) of reintroducing all parts of the compacted cell culture medium obtained in step b1) of claim 1 did not confer a particular inherent property to the dry granulated cell culture medium, but implied that the dry granulated cell culture medium had a particle size larger than 0.5 mm and was dust-free (see page 32, lines 17 to 26).

Even if claim 1 was limited to the use of a dry-granulated cell culture medium obtained by roller compaction, there was no evidence on file that the physical appearance of the resulting granulates contributed to the technical character of the dry cell culture medium. The form of the granulates represented an aesthetic creation under Article 52 (b) EPC. Moreover, claim 1 included embodiments which due to additional downstream processing of the granules had lost said property (see claim 5). The breaking edges were smoothed and/or lost.

Although some of the components, such as salts, cysteine and iron salts, might be subjected to ion exchange and/or a change in their oxidative state, depending on the process used, claim 1 did not require a cell culture medium comprising cysteine or an iron salt, nor a cell culture medium comprising salts which might undergo an ion exchange. Independent of whether the dry cell culture medium in granulated form was prepared by dry granulation or wet granulation, the physical and/or chemical effects reported above would inevitably also occur after the dry cell culture medium in granulated form was dissolved in a solvent as required by claim 1. Moreover, no evidence was provided demonstrating a better dissolution behavior or a better performance during cell culture of a dry-granulated

cell culture medium as compared to a wet-granulated cell culture medium.

The only compound dissolved and spray-dried in the examples of document E1 was sodium bicarbonate, and none of the above-described redox-effects could be ascribed to sodium bicarbonate. The aqueous solution functioned as a film forming binding agent (see document E37, page 30, section 3.7.2), which agglomerated the undissolved dry media particles.

Document E22 related to dry, solid culture media which were suitable for cell and tissue cultures in which the nutritive properties of the individual constituents remained essentially stable. The media could be in granulated form (see pages 4 and 9, last paragraph, respectively). The cell culture medium components of NCTC-109, which did not comprise peptone or tryptone, were disclosed (see pages 11 to 13). The dry cell culture medium was tabletted or pelleted or granulated. However, tablets and pellets could only be obtained by pressure-agglomeration techniques and eventually with roller compaction (see common general knowledge evidenced by E7, page 1632, Figure 2 (d), upper panel; and E36, page 472, section 6.2.2; and E37, pages 119-120). Tablets were redissolved in distilled or deionized water and used for culturing cells (see E22, page 9, lines 3 to 4 from the bottom; Example 1).

Document E39 disclosed a standard bacterial cell culture medium, in which yeast extract was formulated into a peptone- or tryptone-free buffered solution by addition of salts such as calcium carbonate, which further comprised a saccharide such as glucose. Yeast extract was known to encompass amino acids, vitamins, and cofactors, such as biotin and nucleic acids

obtainable after yeast-autolysis (see document E38). This medium could be formulated into a dry granulate as reported in paragraph [0012] of the patent.

Inventive step

Document E1 or alternatively document E22 represented the closest prior art for the the subject-matter of claim 1.

Document E1 disclosed a method for producing a dry cell culture medium comprising the salt and buffering agent sodium bicarbonate. Typical media components were amino acids, salts, vitamins, sugars (i.e. saccharides), nucleic acids and sodium bicarbonate . The combined use of a spray-drying apparatus and a fluid bed apparatus integrated within the drying chamber was used for the production of powders from heat-sensitive formulations of nutritive media. A spray-dried and agglomerated powdered nutritive medium was obtained (i.e. granulated cell culture media).

The difference between document E1 and the subject-matter of claim 1 was that the dry granulated cell culture medium was preparable by a process defined in claim 1 comprising the step of compacting mixed dry powders in a roll press versus wet granulation in document E1. The dry granulation process using roller compaction defined in claim 1 resulted in flakes having breaking edges while wet granulation did not (see document E42).

There was no evidence in the patent that the preparation of dry-granulated cell culture medium avoided side reactions caused by wetting or heating in comparison to a granulated medium prepared by wet

granulation methods.

Since the advantages referred to in paragraphs [0015] and [0016] of the patent, imparted to the dry-granulated cell culture medium compared to cell culture media prepared by wet granulation, lacked an adequate support, the technical problem needed to be formulated as the provision of an alternative cell culture medium in granulated form for use in cell culture.

The proposed solution was a cell culture medium in granulated form exhibiting breaking edges which was preparable by a dry-granulation method defined in claim 1.

Obviousness

The skilled person in this case was a team of a scientists working in the field of cell culturing and a process engineer in the field of chemical engineering who can be expected to look for suggestions in neighbouring fields if the same or similar problems arose in such fields.

The common general knowledge was represented by documents E36 and E37. The knowledge in the neighboring field pertaining to dry granulation was represented by documents E8 and E10. Document E37 related to problems and definitions of compacting by a practical example which used a roller compactor for pressure agglomeration. This process included a step of recycling of the fine particles (see page 144 and seq.). Hence, it formed part of the common general knowledge that different forms of a product could be achieved by applying different granulation techniques.

In consequence, starting from document E1 the claimed solution was obvious.

Document E22 described the provision of sterile, powder like culture media which were suitable for cell culture, in particular of mammalian cells (see page 4, second paragraph). The culture media were in any suitable form such as in the form of "trockenen Pulvern, Granulaten, Pellets" (engl. "dry powders, granulates, pellets") which could later on be redissolved in distilled water (see page 9, last paragraph). There was no deterioration of heat-sensitive substances in the medium as it exhibited the same "cloning efficiency" as "untreated" liquid medium.

Therefore, starting from document E1 and aiming at providing an alternative cell culture medium in granulated form for use in culturing cells, the skilled person would have been guided to a dry cell culture medium in granulated form prepared by dry granulation in light of common general knowledge such as documents E36, E37, and E40 and/or E22.

Alternatively, starting from document E22 as the closest prior art, the subject-matter of claim 1 differed from the tableted cell culture medium disclosed in document E22, in that it was prepared by compaction (i.e. dry granulation), e.g. by preparing pellets or tablets which were then crushed to form the dry granulates (see page 9). The method for preparing the cell culture medium in dry form was not shown to be associated with any effect. Hence, the objective problem resided in the provision of an alternative cell culture medium in dry form for use in a method for culturing cells. The solution of providing a dry cell culture medium in pelleted or granulated form was

suggested in the last paragraph of page 9 of document E22. Thus, the skilled person confronted with the technical problem identified above would use his/her common general knowledge (see documents E7, E36, E37) to prepare another dry cell culture medium in granular form without the use of inventive activity.

XII. The submissions made by the respondent as far as relevant to this decision were essentially as follows:

Claim interpretation

There was no ambiguity in the expression "dry granulated cell culture medium" The use of dry granulated cell culture medium according to claim 1 was not only limited by its preamble but also by the step of compacting said mixed powder in a roll press set out in claim 1. This requirement defined that the dry granulated cell culture medium was clearly a "dry-granulated" cell culture medium, regardless of the presence or absence of a comma or hyphen between the terms "dry" and "granulated".

The "dry-granulated" cell culture medium, due to the pressure between the rolls required for compacting said mixed powder in a roll press, exhibited clod-like fragments or flakes with irregular edges (see document E42). On the other hand, wet granular media produced according to document El were shown to be made up of individual granulate berry-shaped particles (see document E3, Figure 2). A material prepared by a dry granulation process was different in its appearance to one which was prepared by a wet granulation. This was confirmed by document E47 (see page 48, section 4.3).

It was possible, if the composition of the original cell culture medium to be processed was known, to determine through chemical analysis of the cell culture medium whether granules were in contact with water or not during their preparation. The wet granulation process might act on the cell culture medium and modify several properties thereof. Water was indeed known to have an effect on some - more or less stable - components of the original cell culture medium. For example, cysteine might form a dimeric form upon contact with water -cystine. The water solubility of cystine was reduced compared to cysteine. Such modified composition would not be converted back to its original composition by a mere drying step. The same rationale applied to the concentrations of chemical salts which, on contact with water and being dried, would form partially substituted salts at different concentrations with different hydrates. Oxidation states of some metallic ions might change when contacted with dissolved ammonium citrate in water. Dry granulation of the cell culture medium prevented any of these changes.

Sufficiency of disclosure

An objection of lack of sufficiency of disclosure raised under Article 83 EPC presupposed serious doubts substantiated by verifiable facts . Even if the supplementary experimental evidence submitted during examination did not include all the experimental details about how the experiments were carried out (see documents E47 and E48) and none of the examples in the patent used a cell culture medium as defined in claim 1, appellant failed to raise serious doubts substantiated by verifiable facts that the invention could not be readily put into practice.

Novelty

The granulates disclosed in document E1 were obtained by a manufacturing process different from that used in the prior art and had different technical properties. The different physical appearance and a potentially different chemical composition were granted by the different process used. The use of dry compacted cell culture media was not disclosed in document E1. Document E22 did not identify how the cell culture medium was produced. Even if it described to tablet the dry cell culture medium, to pellet same, or to provide it as a granulate, there was nowhere any reference to the use of a dry-granulation method. Document E39 related to a liquid medium and not a dry-granulated medium. Document E46 related to a glucose yeast extract agar. Due to this difference, document E46 could not establish that the medium in document E39 was prior art under Article 54(2) EPC. No document suggested that it was known to use these media as dry granulated media when read in combination with common general knowledge. Thus, claim 1 was novel.

Inventive step

Document E1 represented the closest prior art for the the subject-matter of claim 1.

Document E1 described the preparation and use of wet granulated cell culture media (see page 4, line 27 to page 6, line 19). The cell culture media were prepared in liquid or powder form. Liquid media as recited in document E1 were not stable in storage, whereas powdered media were more stable, but were difficult to handle, because they were often difficult to dissolve and were dusty. Thus, document E1 proposed wet

granulation to optimise these media. Powdered media were contacted with liquid, granulated and then dried (page 32, line 27 to page 33, line 14).

Thus, starting from document E1, the problem to be solved was to provide an at least alternative form of a cell culture medium for use in cell culture.

The solution to the problem was to use cell culture medium that was dry granulated using a roll press in accordance with claim 1.

Neither document E1 nor any other cited prior art document suggested a dry granulation performed by compacting said mixed powder in a roll press.

Although roller compaction was a well-known technology, it was never used in the field of cell culture media and was known not to be applicable to all powders. Document E1 contained no suggestion that it might be beneficial to replace wet granulation.

From documents E2, E8 and E10, belonging to the field of pharmacy, and documents E36 and E37, the skilled person was informed that dry compaction was neither easy nor applicable to all powders. Document E2 recommended the addition of so-called lubricants for the production of tablets. Documents E8, E10, E36 and E37 recommended the addition of binders for compaction to ensure that the powder held together.

The combination of document E1 with E22 failed also to suggest the present claimed invention. Document E22 disclosed that cell culture media could be sterilised in various forms, e.g. tablets, granules, powders, etc. Dry compaction was not mentioned.

Starting from document E22, which dealt with the sterilisation of any type of cell culture media, the skilled person without knowledge of the invention would develop this aspect rather than the method of manufacture of these media. There was no reason starting from document E22 to produce media in a particular way, and certainly not by means of dry compaction.

XIII. Appellant requested that the decision under appeal be set aside and the patent be revoked. It further requested that documents E44 to E46 be admitted into the proceedings.

XIV. The patent proprietor (respondent) requested that the appeal be dismissed or alternatively that the European patent be maintained on the basis of auxiliary requests 2-5. Auxiliary requests 2 to 4 were filed with patentee's submission dated 30 November 2017 during the opposition proceedings. Auxiliary request 5 was filed under cover of a letter dated 6 December 2018 with the patentee's reply to the statement of grounds of appeal. It further requested that documents E47 and E48 be admitted into the proceedings.

Reasons for the Decision

Procedural issues

Basis of the appeal proceedings

1. Appellant stated in its grounds of appeal inter alia: "Contrary to the Opposition Division (OD)'s finding in point 13.3 of the reasons, this ambiguity of claim 1 results in a lack of novelty over the prior art, as already argued in the Opponent's submission under Rule

116 EPC of 16 November 2017, and Opponent's further submission dated 19 December, 2017." (see statement of the grounds of appeal, page 4 last paragraph). Similarly, respondent stated: "Further, reference is made to the submissions of the patent proprietor dated 23.03.2017, 30.11.2017 and 18.01.2018, which are also to be considered for the appeal proceedings." (see respondent's reply to the statement of the grounds of appeal, page 2/9 first paragraph). Both appellants considered these submissions to form part of their appeal case.

1.1 Pursuant to Article 12(2) RPBA 2007, the content of which has remained substantially unamended in Article 12(3) RPBA 2020, the statement of grounds of appeal and the reply to the statement shall contain a party's complete case. This requirement is not fulfilled by a passing reference to the facts and evidence put forward in opposition proceedings (see also "Case Law of the Boards of Appeal of the EPO", 9th edition 2019, V.A. 2.6.3.e), 1169, and V.A.2.6.4.a), 1173).

1.2 Appellant provided no reason why the decision of the opposition division under Article 54 EPC was incorrect in respect of some arguments raised in the opposition proceedings. However, it is for the appellant to put forward in its statement of grounds of appeal its line(s) of argument and each of the facts and evidence on which they want to rely in appeal proceedings. Hence, objections raised in the opposition proceedings which were not adequately substantiated in appeal proceedings are not considered under Article 12(3) RPBA 2020.

Admission of documents E44 to E48 into the appeal proceedings (Article 12(4) RPBA 2007)

2. With the statement of grounds of appeal, appellant submitted new documents E44 to E46 and with its reply to the statement of grounds of appeal, respondent submitted new documents E47 and E48.

2.1 Since no objections were raised against the admission of documents E44 to E48, the board admits them all into the appeal proceedings (Article 12(4) RPBA 2007).

Main Request (claims 1-8 as granted)
Interpretation of claim 1

3. Appellant agued that the expression "dry granulated cell culture medium" in claim 1 was ambiguous. The "dry granulated cell culture medium" could be interpreted either as a cell culture medium which had been subjected to dry granulation or as a dry cell culture medium in granulated form. A dry cell culture medium in granulated form could be prepared by wet granulation as well as dry granulation. The resulting dry medium could not be distinguished.

3.1 The board disagrees with appellant's interpretation. The dry granulated cell culture medium according to claim 1 is not only defined by the preamble of the claim but also by the step of compacting said mixed powder in a roll press as set out in claim 1. The requirement that the dry granulated cell culture medium is preparable by the method steps a), b), b1) and b2) set out in claim 1 clearly defines the medium as a "dry-granulated" cell culture medium. The patent's teaching confirms this view (see patent paragraph [0027]).

3.2 The "dry-granulated" cell culture medium, due to the pressure between the rolls required for compacting said mixed powder in a roll press, exhibits clod-like fragments or flakes with irregular edges (see document E42). On the other hand, wet granular media produced according to document E1 were shown to be made up of individual granulate berry-shaped particles (see document E3, Figure 2). Thus, a material prepared by a dry granulation process is different in its appearance to one which was prepared by a wet granulated material. This is confirmed by document E47 (see page 48, section 4.3). Contrary to appellant's submissions, there is thus a structural feature sufficient to distinguish granules according to claim 1 from granules prepared by a wet-granulation method.

3.3 Even if this property were disregarded, the skilled person would nevertheless be capable of determining, if the composition of the original cell culture medium to be processed was known, through chemical analysis of the cell culture medium, whether granules were in contact with water or not during steps (b1) and (b2) of their preparation.
The wet granulation process may act on the cell culture medium and modify several properties thereof. Indeed, water is known to have an effect on some - more or less stable - components of the original cell culture medium. For example, cysteine may form a dimeric form of cysteine upon contact with water - cystine -. The water solubility of cystine is reduced compared to cysteine. Such modified composition will not be converted back to its original composition by a drying step. The same rationale applies to the concentrations of chemical salts which, on contact with water and then dried, will form partially substituted salts at different concentrations with different hydrates.

Oxidation states of some metallic ions may change when they are contacted with dissolved ammonium citrate in water. Dry granulation of the cell culture medium prevents any of these changes.

Sufficiency of disclosure (Article 100(b) EPC)

4. Appellant argued that the only example of the patent did not fall under the ambit of claim 1. The supplementary evidence submitted by the respondent to address the objection raised under Article 83 EPC during examination was provided with insufficient information to allow the skilled person to reliably and validly reproduce the tests made. Similarly, the evidence submitted with documents E48 and E47 should be disregarded as they did not specify what "according to the specifications of the patent" means.

4.1 Document E41, submitted by the respondent, provided no evidence that the process defined in claim 1 was sufficient to prepare the dry-granulated cell culture medium used in claim 1. Besides, it was unknown whether the media used in document E41 contained saccharides and at least one cofactor.

4.2 Since the patent did not contain an example falling under claim 1 and did not provide sufficient information on how the invention could be put into practice over the entire breadth of the claims, there was only a weak presumption that the invention was sufficiently disclosed. Under these circumstances, it was sufficient for the appellant to show, by plausible arguments, that the skilled person could not put the invention into practice over the full scope of the claim.

4.3 As the composition of the cell culture media, analysed during examination procedure (see document E29 Table 1), always contained saccharides, appellant asserted that the type and content of saccharide was essential, as a binding agent, for the invention to be carried out (see documents E8, page 160, middle of the page; E37, page 30, and E40, paragraph bridging pages 891 and 892).

5. The board considers that the appellant has confined its submissions to mere allegations and has failed to cast serious doubts, substantiated by verifiable facts that the claimed subject matter could be carried out. First the different compositions of the mixtures used in document E29 could all be compacted "according to the method of the invention". Second, a subsequent experiment establishes that a dry cell culture medium with a low content of saccharide, despite the doubts raised by the appellant in its statement of grounds of appeal, could nevertheless be granulated by a process defined in claim 1 (see documents E48 and E47). Although it is accepted that the appellant could not exactly repeat the experiment submitted during the examination proceedings, this is not required. Despite providing no example, the patent specification contains some information of how to put the invention into practice. Thus, there is more than only a weak presumption that the invention is sufficiently disclosed. In the absence of evidence to the contrary, the information in the description, which may be supplemented by the common knowledge, is considered sufficient to enable the skilled person to carry out the invention without undue burden.

5.1 Consequently, the ground for opposition of Article 100(b) EPC does not prejudice the maintenance of the patent.

Novelty (Article 100(a) in conjunction with Article 54 EPC)

6. Appellant asserted that any one of documents E1, E22 and E39 anticipated the subject-matter of claim 1.

6.1 The parties agreed that neither the composition of the medium, nor the step b2) of reintroducing particles of small size into the mixed powder nor how said medium is used could establish novelty (see decision under appeal, item 13.4.1).

6.1.1 Document E1 discloses a method for producing a dry cell culture medium comprising the salt and buffering agent sodium bicarbonate (see page 51, line 12; page 53, lines 14 to 17; and page 57, lines 18 to 21). The cell culture medium is intended for culturing mammalian cells (see page 10, lines 16 to 18). Typical media components are amino acids, salts, vitamins, sugars (i.e. saccharides), nucleic acids and sodium bicarbonate (see page 17, lines 18 to 19, and page 15, lines 16 to 24). Animal cell culture media are for example medium 199, MCDB 131 and MCDB 153. They are free of tryptone and peptone (see documents E32, E33 and E34, respectively) (see page 21, lines 10 to 26). The combined use of a spray-drying apparatus and a fluid bed apparatus integrated within the drying chamber is used to produce powders from heat-sensitive formulations of nutritive media. A spray-dried and agglomerated powdered nutritive medium is obtained (i.e. a granulated cell culture medium)(see Examples 5 and 6 and page 35, line 26 to page 36, line 3).
The step b2) of reintroducing all parts of the

compacted cell culture medium obtained in step b1) of claim 1 does not confer a particular inherent property to the dry granulated cell culture medium, but implies that the dry granulated cell culture medium has a particle size larger than 0.5 mm and is dust-free.

6.1.2 Document E22 relates to a process for the sterilisation of culture media and "relates to a novel, sterile, essentially dry, solid culture medium which is suitable for cell and tissue cultures and in particular a sterile, dry, solid multicellular culture medium from animal cells and, in particular, from mammalian cells, in particular for in vitro cultures in which the activity and the nutritive properties of the individual constituents remain essentially stable." (see page 4, last paragraph). Although the sterilization of culture media by exposure to high energy radiation is applicable on any physical form such as solids, dry powders, granules, pellets and the like, irradiation is preferably applied on culture media in powder or tablet form (see claims 6 and 9; page 9, last paragraph).

6.1.3 Document E39 discloses a standard bacterial cell culture medium, in which yeast extract is formulated into a peptone- or tryptone-free buffered solution by addition of salts such as calcium carbonate, which further comprises a saccharide such as glucose. Yeast extract was known to encompass amino acids, vitamins, and cofactors, such as biotin and nucleic acids obtainable after yeast-autolysis (see document E38).

6.2 The board considers that the expression "dry granulated cell culture medium" as used in claim 1 can only be interpreted as "dry-granulated" cell culture medium (see items 3.1 to 3.3 above).

6.3 The granulates disclosed in document E1 are obtained by a different manufacturing process from that used in claim 1. The process step of compacting "said mixed powder in a roll press" as set out in claim 1 provides granulates which can be distinguished by means of at least one structural or functional technical feature from the granulates obtained by the fluid bed technology used in document E1.

As stated above, the dry-granulated cell culture medium, which does not comprise peptones or tryptones, prepared according to claim 1, has breaking edges (see document E42; document E3, Figure 2) whereas wet granular media produced according to document E1 are made up of individual granulate berry-shaped particles. Thus, a material prepared according to claim 1 differs at least in appearance from the wet granulated material as described in document E1. This is confirmed by document E37 (see page 48, section 4.3).

As further stated above, the dry cell culture medium obtainable by the process defined in claim 1 may also be chemically distinguishable from a medium obtained by wet granulation with respect to the concentrations of its chemical salts, its hydrates, the oxidation status of metallic ion in salts observed before and after solubilization and/or with respect to the concentration of heat- or solubilization-sensitive components in a different form detected before and after having been contacted with water and being dried.

6.4 Appellant contended that the breaking edges of the dry-granulated cell culture medium represented a non-technical feature, i.e. an aesthetic creation excluded from patentability under Article 52(1)(2) EPC.

Reference was made to decision T 2050/07 of 19 February 2013 (reasons 9 to 13).

6.5 Decision T 2050/07 mentioned that if the distinguishing features are of a non-technical nature - a mathematical method or a method for performing mental activities - and, in accordance with established case law, do not contribute to the technical character of an invention and do not interact with the technical subject-matter of the claim for solving a technical problem, they should be ignored when assessing novelty.

6.6 The board considers that the different forms of the resulting granules directly preparable by the process of claim 1 or a wet granulation process represent a structural technical difference of the granules. This is a direct consequence of the technical process used. It is the process for preparing the dry granulated cell culture medium which contributes to the technical character of the invention and imparts to the dry granulated cell culture medium the technical properties necessary for solving the technical problem.
There is no indication that dry granulated cell culture medium prepared by the process of claim 1 including further milling steps would lose its technical properties. The shape of the dry granulated cell culture medium may act as an indicator of the process used.

Thus, the breaking edge of the dry granulates prepared by the method defined in claim 1 constitutes a distinguishing structural technical feature over the prior art that cannot be ignored. Decision T 2050/07 supports the board's findings.

6.7 Since document E22 does not describe how the dry cell culture media were obtained, it cannot anticipate the use of a dry-granulated cell culture medium preparable by the process defined in claim 1.

6.8 Document E39, whose publication date could not be ascertained, discloses a liquid medium. Document E46 relates to a glucose yeast extract agar. The content of document E39 which refers to a liquid medium, unlike a "dry-granulated" cell culture medium, can therefore not anticipate the use according to claim 1.

6.9 Thus, documents E1, E22 and E39 do not disclose the use of a dry granulated cell culture medium as defined in claim 1. The subject-matter of the main request is novel.

Inventive step (Article 100(a) in conjunction with Article 56 EPC)

The closest prior art

7. It was common ground between the parties that document E1 represents the closest prior art for the subject-matter of claim 1.

8. Document E1 discloses a method for producing a dry powder cell culture medium comprising the salt and buffering agent sodium bicarbonate. Typical media components are amino acids, salts, vitamins, sugars (i.e. saccharides), nucleic acids and sodium bicarbonate . A spray-drying apparatus and a fluid bed apparatus integrated within the drying chamber is used for the production of powders from heat-sensitive formulations of nutritive media. A spray-dried and

agglomerated powdered nutritive medium is obtained (i.e. granulated cell culture media).

8.1 The difference between document E1 and the subject-matter of claim 1 is that the dry granulated cell culture medium is preparable by a process comprising the step of compacting mixed dry powders in a roll press versus wet granulation in document E1. The dry granulation process using roller compaction defined in claim 1 results in flakes having breaking edges while wet granulation does not (see document E42).

8.2 The technical problem must be determined on the basis of objectively established facts, which means that for the determination of the objective technical problem only the effects actually achieved vis-à-vis the closest prior art can be taken into account. Nor can any alleged advantage referred to in the patent be taken into account in determining the problem underlying the invention if the comparison with the closest prior art is not sufficiently demonstrated.

8.2.1 The board considers that there is no evidence in the patent that the preparation of dry-granulated cell culture medium avoids side reactions caused by wetting or heating in comparison to a granulated medium prepared by wet granulation methods (see paragraphs [0015] and [0016]). Document E1 discloses that instable components were admixed to powdered nutritive media for producing agglomerated nutritive media without being destroyed (see bridging paragraph on page 31 and 32). The use of an agglomerated powdered cell culture medium with water or serum provides evidence that the fluid bed technology (wet granulation) had no detectable adverse effect on the heat sensitive fetal bovine serum (see Example 11).

8.2.2 Since the advantages referred to in paragraphs [0015] and [0016] of the patent, imparted to the dry-granulated cell culture medium compared to the cell culture media prepared by wet granulation method, are not proven, they are not taken into account.

8.2.3 The difference in the form of the granulates produced by dry granulation versus wet granulation may be an indicator of a technical process allowing at best to identify the method by which said agglomerate was produced (see document E37). Nowhere was it demonstrated that the form of the granulate alone provides a technical effect.

8.2.4 In consequence the objective technical problem in view of document E1 may be formulated as the provision of an alternative cell culture medium in granulated form for use in cell culture.

8.3 The solution is a cell culture medium as defined in claim 1.

Obviousness

8.4 The question to be answered is whether, starting from the method for producing a dry powder cell culture medium disclosed in document E1, the skilled person, would have been motivated to solve the technical problem by providing a dry-granulated cell culture medium - which does not comprise peptones or tryptones- that is preparable by compacting a mixed powder using a roll press and including a step of reintroducing fine particulates.

8.5 The skilled person in this case is a team of a scientists working in the field of cell culturing and a process engineer in the field of chemical engineering who can be expected to look for suggestions in neighbouring fields if the same or similar problems arise in such fields (CLBA, I.D.8.1.1, of the 9th ed. on page 203, second paragraph).

8.5.1 The common general knowledge is represented by documents E36 and E37. The knowledge in the neighboring field pertaining to dry granulation is represented by E8 and E10. Document E37, relates to problems and definitions of compacting by a practical example, which uses a roller compactor for pressure agglomeration. This process includes a step of recycling of the fine particles (see page 144 and seq.).

8.6 Appellant argued that starting from document E1, the skilled person was guided to a dry cell culture medium in granulated form prepared by dry granulation in the light of common general knowledge such as documents E36, E37, and E40 and/or in light of document E22.

8.6.1 The board disagrees. Document E1 provides no incentive for the skilled person to turn to documents E2, E8, E10 or E37 and E36.

8.6.2 Document E2 refers to nutritional supplements and/or pharmaceutical compositions comprising an embedded lubrication matrix. Document E8 refers to a roller compaction technology among many other granulation technologies. Document E10 reviews the progress and the use of roll compaction/dry granulation in the production of directly compressible excipients, the compaction of drugs and drug formulations, the granulation of inorganic materials, the granulation of

dry herbal material. Document E37 discloses under "Stoffzusammensetzung" ("Material composition") that the advantage of agglomeration can be cancelled out by certain techniques used in the agglomeration process. These adverse effects should be taken into account in the selection of the agglomeration process. Examples of this can be found in the food and animal feed industries. Document E36 with the title "Manual of mechanical process engineering" refers at best to mixed fertiliser (see Table 6.3). None of them suggests to use dry compaction of mixed powders in a roll press for the production of cell culture media.

8.6.3 On the other hand, the board observes that documents E2, E8, E10, E36 and E37 neither point to nor otherwise suggest that dry compaction using a roll press of mixed powders forming a peptone- or tryptone-free cell culture medium, was ever envisaged or proposed as an alternative to the wet-granulated agglomeration techniques, let alone that the use of this technique would result in a dry-granulated cell culture media for use in cell culture with a reasonable expectation of success. Even if the skilled person could have compacted the mixed powders using a roll press, there is no identifiable reason in any of these documents why he should have done so in the hope of solving the underlying technical problem.

8.7 The board considers that since neither the implementation nor the production of a dry-granulated cell culture medium preparable by the method defined in claim 1 was envisaged or suggested by any of the prior art documents, the skilled person was also never in a "try and see" situation.

8.8 Hence, the skilled person finds no motivation in any of documents E2, E8, E10 or E37 and E36 to combine their teaching with that of document E1 so as to arrive at the method of claim 1 in an obvious manner other than with hindsight.

8.9 The board disagrees that the skilled person starting from document E1 would have been guided to a dry cell culture medium in granulated form prepared by dry granulation in the light of document E22.

8.10 Document E22 relates to a process for sterilising culture media and to a novel, sterile, essentially dry, solid culture medium which is suitable for cell and tissue cultures (see page 4, last paragraph). Even if the culture media described in document E22 can be in any suitable form of "trockenen Pulvern, Granulaten, Pellets" (engl. "dry powders, granules, pellets"), where the pellets can later be redissolved in distilled water, document E22 does not describe how the dry culture media are obtained, and since no process of preparing dry cell culture media is mentioned in document E1, there can be no indication of how the dry culture media were obtained either.

9. The appellant considered document E22 to represent an alternative starting point for the assessment of inventive step.

9.1 Starting from document E22 the skilled person, faced with the technical problem of providing an alternative cell culture medium in dry form for use in cell cultivation, would have prepared a dry granulated cell culture medium according to the process defined in claim 1. This finding also applied to the combination

of document E22 with documents E36, E37 and E40 and/or document E1.

9.2 The board disagrees. Even if the appellant was not aware of any other way of producing tablets than by pressure agglomeration and the opposition division provided no evidence for any further alternative way for preparing tablets, document E22 does not disclose that the tablets were inevitably compacted by a dry-granulation of mixed powders by the process defined in claim 1 using a roll press rather than by any other pressure agglomeration techniques.

9.3 Even if the skilled person could have prepared the dry granulated cell culture medium according to the process defined in claim 1, in the absence of any clear indication or suggestion in document E22, which does not even describe how the dry culture media were obtained, there is no reason why he/she would have done so.

9.4 Even if document E22 on page 9 describes "irradiation of dry powders, granules and pellets", it remains unclear why this statement should prompt the skilled person, trying to obtain a dry cell culture medium in granular form, to turn to pressure agglomeration techniques, in particular to dry-granulation compaction techniques using mixed powders in a roll press, rather than wet granulation techniques.

9.5 In view of the above considerations, the board concludes that the claimed subject-matter of claim 1 would not have been obvious to the skilled person and accordingly involves an inventive step. The same applies to the dependent claims. The subject-matter of the main request involves an inventive step.

10. Consequently, the ground for opposition of Article 100(a) in conjunction with Articles 54 and 56 EPC does not prejudice the maintenance of the patent.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

L. Malécot-Grob B. Stolz

Decision electronically authenticated