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Datasheet for the decision of 26 February 2026

Case Number: T 0150/24 - 3.3.08

Application Number: 14780959.4

Publication Number: 3047013

IPC: C12M1/00

Language of the proceedings: EN

Title of invention:
METHODS AND SYSTEMS FOR PROCESSING A CELL CULTURE

Patent Proprietor:
Genzyme Corporation

Opponent:
König Szynka Tilmann von Renesse

Headword:
Methods for processing a cell culture/GENZYME

Relevant legal provisions:
EPC Art. 56

Keyword:
Main request and auxiliary request 2 - Inventive step - (no)

Decisions cited:

Catchword:

Europäisches Patentamt
European Patent Office
Office européen des brevets

Beschwerdekammern

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Case Number: T 0150/24 - 3.3.08

D E C I S I O N
of Technical Board of Appeal 3.3.08
of 26 February 2026

Appellant II: (Patent Proprietor)	Genzyme Corporation 50 Binney Street Cambridge, MA 02142 (US)
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Appellant I: (Opponent)	König Szynka Tilmann von Renesse Patentanwälte Partnerschaft mbB Mönchenwerther Strasse 11 40545 Düsseldorf (DE)
Representative:	Hemsath, Lars Hoffmann Eitle Patent- und Rechtsanwälte PartmbB Arabellastraße 30 81925 München (DE)
Decision under appeal:	**Interlocutory decision of the Opposition Division of the European Patent Office posted on 27 November 2023 concerning maintenance of the European Patent No. 3047013 in amended form**

Composition of the Board:

Chairwoman	T. Sommerfeld
Members:	D. Pilat
	A. Bacchin

Summary of Facts and Submissions

I. European patent No. 3 047 013 is based on European patent application No. 14 780 959.4, filed as an international application published as WO 2015/039115. The patent was opposed on the grounds of Article 100(a) EPC in conjunction with Articles 54 and 56 EPC, and of Article 100(c) EPC. The opposition division held that the claims of the main request contravened Article 56 EPC, while the patent could be maintained on the basis of the claims of auxiliary request 1 which complied with the requirements of the EPC.

II. Both the opponent and the patent proprietor (appellants I and II, respectively) lodged an appeal against the decision of the opposition division. With their grounds of appeal, appellant II submitted a main request and auxiliary request 1, which correspond to auxiliary requests 6 and 7, respectively, filed during opposition with letter of 18 August 2023, as well as auxiliary request 2, corresponding to the auxiliary request which was found allowable by the opposition division. At oral proceedings before the board, appellant II withdrew auxiliary request 1.

III. Claim 1 of **the main request** reads as follows:

"1. A method of processing a cell culture, the method comprising:

(a) providing an open circuit filtration system comprising a bioreactor comprising a cell culture, a tangential flow filtration (TFF) unit having first and second inlets, a first conduit in fluid communication between the bioreactor and the TFF unit first inlet, and a second conduit in fluid

communication between the bioreactor and the TFF unit second inlet, and at least one pump disposed within the system for flowing fluid through the system, wherein the system is configured such that fluid can be flowed reversibly through the system from or to the bioreactor and through the first and second conduits and the TFF unit via the at least one pump, and filtrate can be collected from the TFF unit; wherein the TFF unit comprises a tubular cross-flow filter;

(b) flowing cell culture from the bioreactor through the first and second conduits and the TFF unit in a first flow direction for a first period of time,

(c) reversing the first flow direction and flowing the cell culture through the first and second conduits and the TFF unit in a second flow direction for a second period of time;

(d) reversing the second flow direction and flowing the culture through the first and second conduits and the TFF unit in the first flow direction for a third period of time;

(e) repeating steps (c) - (d) at least two times; and

(f) collecting the filtrate."

IV. Claim 1 of **auxiliary request 2** differs from claim 1 of the main request in that it adds at the end of the claim "wherein the cell culture contains a plurality of mammalian cells suspended in a liquid culture medium and a secreted recombinant protein, e.g., an antibody of antigen-binding fragment thereof, a growth factor, a cytokine, or an enzyme and the filtrate contains the secreted recombinant protein".

V. The documents cited in this decision include the following:

D2a English translation of T. Asakura & K. Toda Hakkokogaku Kaishi, Vol. 69(4), pages 225 to 232 (1991)
D10 M-F. Clincke *et al.* Biotechnol. Prog. Vol. 29 pages 768 to 777 (2013)
D13 C.G. Smith *et al.* Bioprocess Engineering Vol. 6, pages 213 to 219 (1991)
D14 G. Belfort *et al.* Journal of Membrane Science Vol. 96, pages 1 to 58 (1994)

VI. The parties' submissions, insofar as they are relevant to the decision, are discussed in the Reasons for the Decision, below.

VII. The parties' final requests, insofar as relevant for the present decision, were the following:

Appellant I requested that the decision be set aside and amended such that the patent be revoked.

Appellant II requested that the decision be set aside and that the patent be maintained based on the claims of the main request filed with the grounds of appeal; alternatively, they requested that the opponent's appeal be dismissed and the patent be maintained on the basis of auxiliary request 2.

Reasons for the Decision

Main request
Inventive step (Article 56 EPC)

1. The claimed invention concerns a method of processing a cell culture which uses an open circuit filtration system with reversible tangential flow across a cross-

flow filter. According to the patent (e.g. paragraph [0006]), the system as claimed, as opposed to conventional unidirectional open circuit or bidirectional closed circuit filtration systems, improves bioprocess performance by increasing viable cell density, increasing percentage viable cells, increasing specific and/or volumetric productivity, increasing specific glucose consumption, and decreasing filter fouling.

Closest prior art and distinguishing feature

2. Document D13 may be considered the closest prior art. It was undisputed that the claimed subject-matter differed from the method disclosed in document D13 in that it uses a particular form of perfusion cultivation with tangential flow filtration (TFF) technology, namely rTFF, wherein the flow direction in the TFF circuit (across the filter) is reversed several times during the process, while D13's method uses conventional TFF, with an unidirectional flow.

Technical effect and objective technical problem

3. In agreement with appellant I and in disagreement with appellant II, for the reasons explained in the following, the board considers that no technical effect can be attributed to this distinguishing feature, because any alleged improvement over the closest prior art was not supported by suitable factual evidence establishing a causal link with the distinguishing feature. As such, no effect can be taken into account when formulating the technical problem in relation to the closest prior art (Case law of the Boards of Appeal of the European Patent Office 11th edition 2025 hereinafter "Case Law" I.D.4.3.1).

4. Appellant II essentially argued that Example 1 of the patent (and Figure 16) provided evidence for an improvement of cell specific productivity obtained by the claimed method in relation to that obtained by the method of D13. In Example 1, it was established that a method using an rTFF perfusion system, as in claim 1, achieved an increased cell specific productivity compared to that in a cell culture using an alternating tangential flow (ATF) perfusion system. Although admittedly this example allowed no direct comparison between the claimed method and that of document D13, appellant II nevertheless argued that, because ATF was shown to be more efficient than TFF (D10, Figure 7 on page 774), it could be indirectly concluded that the claimed method, providing for a higher productivity than that obtained with ATF, would necessarily also have an increased productivity over the method of D13 that used conventional TFF.

5. The board disagrees with appellant II's conclusion. As argued by appellant I, the ATF used in Example 1 and the conventional TFF system described in D13 do not only differ in the periodical reversal of the flow but rather also in other characteristics. Hence, it cannot be excluded that the alleged higher productivity of the claimed TFF system compared to a standard ATF system may be based on technical features which are specific for ATF systems, such as the diaphragm pump, the larger external volume of the cell culture and the longer residence time outside of the bioreactor of the cell culture compared to TFF systems. In any case, it cannot be attributed to the distinguishing feature to D13, namely the periodical reversal of the flow alone rather than to any other technical features. Hence, Example 1

on its own does not provide evidence for an improvement over the closest prior art.

6. The conclusions drawn by appellant II, that D10 allows to conclude that ATF leads to increased cell specific productivity in comparison to TFF, are not persuasive either. D10 compares TFF and ATF, both as microfiltration (MF) or ultrafiltration (UF), in the context of monoclonal antibody (MAb) production. Contrary to appellant II's conclusions, Table 2 of D10 shows an increase of cellular production of 10% for the TFF system in relation to the ATF system; because the cell densities are maintained identical in both systems, the cellular production is in fact a measurement of cell specific productivity. On the other hand, the statement on page 776, column 1, section "Conclusions", that TFF was less favourable for the production of MAb than ATF, is not interpreted as meaning that there was less cell specific productivity with MF TFF than with MF ATF: as can be derived from the observations which precede this statement, the cause for this difference in yield was MAb retention, which was higher for TFF than for ATF in the context of MF but not in the context of UF; the problem was therefore not TFF-specific. Likewise, the board fails to see that the data in Figure 7c show a higher cell-specific productivity for a cell culture using an ATF system in comparison to a cell culture using a TFF perfusion system; even appellant II admitted that the plots were too crowded to confirm a difference. D10 indeed concludes that these values are comparable in all the ATF and TFF runs (page 775, column 1 last full paragraph).

7. Finally, appellant II argued in writing that, starting from D13, the technical effect attributed to the

distinguishing feature was an improvement in productivity profiles (i.e. volumetric and specific productivity) and/or enhanced performance in preventing filter fouling. However, neither the data presented in Example 1, including Figures 15 and 16, nor any other evidence on file demonstrates that such an improvement can be attributed to the periodical reversal of the flow. Consequently, the board's reasoning and conclusion with respect to the absence of a demonstrated effect on cell-specific productivity must also apply to volumetric productivity as well as to the alleged prevention of filter fouling.

8. Hence, the objective technical problem starting from D13 has to be formulated as the provision of an alternative method of cell culture in perfusion bioreactors and the board is satisfied that the method of claim 1 solves this technical problem.

Obviousness

9. Starting from document D13 and faced with the technical problem identified above, the skilled person would look for alternative cell culture systems and would come across the method of D2a, which is almost identical to the one of D13, but for its periodical reversing of the flow direction through the TFF unit. By combining the system disclosed in D13 with the disclosure of D2a, teaching periodic reversion of circulating flow in cross-flow filtration, the skilled person would have arrived at a method according to claim 1 in an obvious way. No pointer or motivation would be required to arrive at any specific alternative system to that of D13.

10. Appellant II argued that the skilled person would not combine D13 with D2a because the latter was not aimed at recombinant protein production using mammalian cells but instead at ethanol production using yeast cells. Since protein molecules are more prone to be retained by the filter than ethanol and yeast cells, being in general smaller than mammalian cells, and therefore also more prone than larger mammalian cells to occlude the filter pores, the skilled person would not have considered using the system of D2a for the method of D13, since it would have expected filter clogging and fouling. In Figure 5 of D2a, it was apparent that only 20% of the initial flux was maintained after 50 hours; such a level of performance would be insufficient for long-term recombinant protein production in perfusion cultures. Moreover, D2a used a membrane filter with a specific pattern for the flow channel which was different from the tubular cross-flow filter (e.g. hollow fiber) used in the method of claim 1 (and of D13 or D10).

11. The board considers that the arguments above relate all to alleged prejudices. However, according to the boards' established case law, each party to the proceedings bears the burden of proving the facts it alleges. It is therefore incumbent on appellant II to demonstrate that these prejudices were genuine and that they would have deterred the skilled person from combining the teaching in D13 with those of document D2a. No evidence was provided to this effect.

12. For the sake of argument, the board considers that even if the skilled person had concerns in view of the difference in size between yeast and mammalian cells, it would only have needed to adjust the perfusion culture and filtration parameters accordingly. While

the cell size may affect filter clogging and fouling if the flow rate is too low, this effect is independent from that caused by a reversal of flow.

13. Although it is undisputed that ethanol is smaller than proteins and soluble, this argument does not take into account the fact that the yeast culture medium in method D2a contains also proteins, which are just as likely to remain trapped on the filter as those described in the claimed method.

14. As regards the assertion that flow reversal produces only a minor effect and would not have been combined with the method of D13, the board notes that the periodic flow reversal does nevertheless result in a fivefold increase in the filtration flux compared with unidirectional flow. In any event, claim 1 does not specify any minimum amplitude or duration for this effect (D2a, Figure 5, page 7/14, lines 2 to 6).

15. It was known that cake layer formation is a general problem in cross-flow filtration irrespective of the filter geometry (D14, page 13, right-hand column, paragraph 1.7) and there is no evidence demonstrating that a reduction of filter fouling could be attributed to the periodic reversal of the flow direction and the use of a straight flow channel.

16. Appellant II moreover argued that it was well known in the art that filtration of cell cultures commonly suffers from filter clogging caused by cells, debris, and biomolecules, leading to reduced filtration efficiency and lower protein yield. Document D13 proposed several alternatives for preventing these problems (page 216, paragraph bridging left-hand and right-hand column), so there would be no reason for the

skilled person to turn to D2a, which showed that flow reversal had only a minor effect.

17. The board considers that, even if document D13 may refer to other alternatives, the skilled person would have needed no incentive to select a method other than that already disclosed in D13 to solve the technical problem identified above. Selecting a method, such as the one disclosed in D2a, from among all the equal alternatives known in the prior art is arbitrary and requires no pointer or incentive. This selection cannot constitute the basis for acknowledging an inventive step.

18. Accordingly, the subject-matter of claim 1 of the main request does not fulfil the requirements of Article 56 EPC.

Auxiliary request 2

19. Claim 1 of auxiliary request 2 is identical to claim 1 of the main request except that it further specifies that the cell culture contains a plurality of mammalian cells suspended in a liquid culture medium and the filtrate contains a secreted recombinant protein (see point IV. above).

20. Claim 1 of auxiliary request 2 fails to further distinguish the claimed method from the one disclosed in D13. D13 itself refers to a homogeneous perfusion culture of mammalian hybridoma cells for producing monoclonal antibodies. As none of these additional features constitute a difference in relation to D13, no technical effect can be associated with them based on which a new technical problem could be formulated. It follows that the reasons for lack of inventive step

developed above for claim 1 of the main request also apply to auxiliary request 2.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The patent is revoked.

The Registrar: The Chairwoman:

C. Rodríguez Rodríguez T. Sommerfeld

Decision electronically authenticated