BESCHWERDEKAMMERN DES EUROPÄISCHEN PATENTAMTS | BOARDS OF APPEAL OF THE EUROPEAN PATENT OFFICE | CHAMBRES DE RECOURS DE L'OFFICE EUROPEEN DES BREVETS

Internal distribution code:
(A) [ ] Publication in OJ
(B) [ ] To Chairmen and Members
(C) [C] To Chairmen

D E C I S I O N
of 31 July 1998

Case Number: T 0373/94 - 3.3.2

Application Number: 86309761.4

Publication Number: 0227401

IPC: A61L 2/06

Language of the proceedings: EN

Title of invention:
Method of producing prefilled sterile plastic syringes

Patentee:
Mallinckrodt, Inc. (a Delaware corporation)

Opponent:
Arzneimittel GmbH Apotheker Vetter & Co.
Bracco S.p.A.

Headword:
Prefilled plastic syringe/MALLINCKRODT

Relevant legal provisions:
EPC Art. 52(1), 56, 83

Keyword:
"Novelty, yes"
"Sufficiency, yes"
"Inventive step, no: the same level of skill has to be applied when, for the same invention, the two questions of sufficient disclosure and inventive step have to be considered"

Decisions cited:
T 0062/82, T 0192/82, T 0254/86, T 0060/89, T 0163/89, T 0641/89, T 0005/91, T 0219/90, T 0943/92

Catchword:
-

Europäisches Patentamt | European Patent Office | Office européen des brevets

Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0373/94 - 3.3.2

D E C I S I O N
of the Technical Board of Appeal 3.3.2
of 31 July 1998

Appellant: (Proprietor of the patent)
Mallinckrodt, Inc. (a Delaware corporation)
675 McDonnell Boulevard
P.O. Box 5840
St. Louis
Missouri 63134 (US)

Representative:
Barry, Robert Stewart Wilson
Eversheds
Senator House
85 Queen Viktoria Street
London EC4V 4JL (GB)

Respondent: (Opponent)
Arzneimittel GmbH Apotheker Vetter & Co.
Schützenstr. 99/101
88212 Ravensburg (DE)

Representative:
Dziewior, Joachim, Dipl.-Phys. Dr.
Patentanwälte
Dr. Hermann Fay
Dr. Joachim Dziewior
Postfach 1767
89007 Ulm (DE)

Opponent:
Bracco S.p.A.
Via E. Folli, 50
20134 Milano (IT)

Representative:
Uexküll & Stolberg
Patentanwälte
Beselerstrasse 4
22607 Hamburg (DE)

Decision under appeal: **Decision of the Opposition Division of the European Patent Office posted 2 March 1994 revoking European patent No. 0 227 401 pursuant to Article 102(1) EPC.**

Composition of the Board:

Chairman: P. A. M. Lançon
Members: G. F. E. Rampold
M. B. Günzel

Summary of Facts and Submissions

I. European patent No. 0 227 401 comprising four claims was granted in response to European patent application No. 86 309 761.4.

The only independent claim has the following wording (reference signs (a) to (h) added):

A method of producing a prefilled, sterile plastic syringe having a molded plastic barrel with an open end and a nozzle at the opposite end, a tip seal closing the nozzle and a piston slidable in the barrel and sealing the open end of the barrel to retain a liquid therein; the method comprising the steps of:

(a) removing debris and other contaminants from the tip seal and piston;

(b) destroying microbial contaminants on the tip seal and piston;

(c) washing the barrel with a sequence of a multiplicity of jets of water to remove debris and pyrogens from the barrel;

(d) applying a lubricant to the tip seal, piston and barrel;

(e) assembling the tip seal on the nozzle of the barrel;

(f) filling the barrel through its open end with a desired quantity of liquid material;

(g) assembling the piston in the open end of the barrel after the filling thereof to complete the enclosure and sealing of the syringe and its contents; and

(h) autoclaving the assembled and sealed syringe to sterilise the plastic syringe and its contents, while maintaining a pressure on the outside surfaces of the syringe at least equal to the pressure of the syringe contents during autoclaving.

The independent claim is followed by dependent claims 2 to 4 relating to specific embodiments of the invention as defined in claim 1.

II. Notice of opposition to the patent was filed

(i) by Respondents (Opponents) 01 under Article 100(a) EPC requesting that the patent be revoked in its entirety, on the ground that the subject-matter of the patent was not patentable within the terms of Articles 52 to 57 EPC; and

(ii) by Respondents (Opponents) 02 under Article 100(a) and (b) EPC requesting that the patent be revoked in its entirety on the grounds of insufficiency (Article 83 EPC) and lack of inventive step (Articles 52(1), 56 EPC).

Out of the 8 citations relied on by the Respondents in support of their requests in the course of the first instance opposition proceedings, the following were considered in the decision of the Opposition Division and are also referred to in this decision:

(1) E. Venten, J. Hoppert, "Eine neue Anlage zur Verarbeitung von Spritzampullen", in Pharm. Ind. 40, 6, 1978, 665-671

(5) Fedegari Autoclavi Sp.A., 27010 Albuzzano (PV), "Perche questo nuovo sistema di sterilizzazione?", 1981; and translation into English.

III. By its decision issued on 2 March 1994 the Opposition Division revoked the patent under Article 102(1) EPC.

In the above decision, the Opposition Division held that the novelty of the subject-matter of the contested patent had to be acknowledged, since none of the cited documents disclosed a method of producing a prefilled, sterile plastic syringe including the step of terminally autoclaving the assembled and sealed syringe to sterilise the plastic syringe and its contents.

As far as inventive step was concerned, the Opposition Division referred to citation (1), which already described a method and means for the manufacture of prefilled glass syringes, including their terminal sterilisation, by subjecting the assembled, filled and sealed syringe to autoclaving while maintaining an appropriate counterpressure in the sterilisation zone. Given this closest state of the art, the problem the invention set out to solve as seen by the Opposition Division was that "of following the trend of the time by producing plastic syringes instead of glass syringes to avoid the fragility of glass and to produce with lower costs."

In the opinion of the Opposition Division, the skilled person seeking a solution to this problem in the state of the art would have come across the technical information in citation (5) describing a series of superheated water shower autoclaves which were

specifically designed for the sterilisation of solutions contained in plastic containers associated with problems of deformation or sealing due to the overpressure, such as plastic vials, jars, and so on. Prefilled plastic syringes were held to fall into this particular category of plastic containers. In particular, the problem of compensating the overpressure formed in the filled plastic containers during autoclaving was found to have been solved already in (5) by maintaining a proper counterpressure of sterile air in the autoclave and thus in exactly the same manner as proposed in claim 1 of the contested patent.

It was further held in the above decision that the necessity of maintaining a sterile, sliding seal between the piston head and the inside surface of the plastic barrel during autoclaving of the syringe would not have been perceived by the skilled person to cause a problem, since this problem as such had already been solved in the manufacture of the prefilled syringes in (1) by an appropriate regulation of both the temperature and pressure in the sterilisation zone.

On this basis the Opposition Division was of the opinion that lack of inventive step prejudiced the maintenance of the patent pursuant to Article 100(a) in conjunction with Article 56 EPC.

Since the patent had to be revoked already on the afore-mentioned grounds, the Opposition Division dispensed with deciding on the issue of insufficiency (Articles 100(b), 83 EPC) raised as a further ground for opposition. It expressed nevertheless in the above

decision its opinion that this ground taken individually was apparently not sufficiently substantiated and supported by the submissions of Respondents 02 to possibly prejudice the maintenance of the patent.

IV. Notice of Appeal was lodged by the Appellants (Patentees) against the decision of the Opposition Division and the statement setting out the grounds of appeal was filed within the time limit set in Article 108 EPC.

V. In the course of the appeal proceedings, Respondents 02 additionally filed the following evidence and requested its admission into the proceedings:

(9) K. Ruig, Le stérilisateur continu hydrostatique "Pharma-Hydromatic" pour la stérilisation des sérums physiologiques en bouteilles de verre et emballages de plastique in Pharma Int. 5/72, 1972, 10-16

(9a) Edition in English language of citation (9) in Pharma Int. 5/72, 1972, 9-14 Since the information provided in both documents (9) and (9a) is identical, the present decision relies hereinafter on the latter written in the language of the proceedings.

(11) Original package of a blood sampling kit for blood gas measurement manufactured and sold under the tradename PREZA PACK by Terumo Corp., Ltd., Tokyo; written description of the PREZA PACK blood sampling kit in product information literature and in the product packaging, 1976, including their translation into English;

(12) US-A-3 902 491

VI. The Appellants' submissions in support of their requests, both in the written procedure and at the oral proceedings, can essentially be summarised as follows:

The decision of the Opposition Division was based upon certain factual errors and a misinterpretation of the state of the art based on hindsight.

In particular, the crucial difference between the closest prior art, viz. citation (1), on the one hand, relating to prefilled glass syringe ampoules, and the patent, on the other, relating to prefilled plastic syringes, was oversimplified and incorrectly appreciated.

Although the method of terminally autoclaving prefilled glass syringes using a proper counterpressure in the sterilising zone was disclosed in citation (1) already in 1978, terminal heat sterilisation was not viewed by the skilled person as a practical solution to the sterilisation of plastic prefilled syringes before the present invention was made available in 1985. The problems perceived by the skilled person and the general prejudice against heat-sterilising plastic syringes explained why there was a delay of 7 years between the publication date of (1) and the patent. If the solution had been obvious, it would have been reached much sooner.

The Opposition Division had also ignored relevant common general knowledge in the field. In view of the fact that terminal heat sterilisation was known to be capable of achieving a significantly increased sterility assurance level, as compared to aseptic filling, the question arose why in the state of the art prefilled plastic syringes were consistently produced by aseptic filing processes. Apart from the fact that

prior to the patent in suit there was no manufacturing process available in the state of the art for producing terminally heat-sterilised prefilled plastic syringes, even unfilled plastic syringes and their parts were, contrary to the opinion of the Opposition Division in the impugned decision, not normally autoclaved, but were sterilised by the use of non-heat methods only, such as ethylene oxide gas or radiation. The common general knowledge prior to the contested patent was that syringes made from glass, on the one hand, would be autoclaved for sterilisation in view of their heat resistance up to 700°C, whereas syringes made from plastic, on the other, would be subjected to non-heat sterilisation methods in view of their considerably reduced heat resistance.

Citation (12) provided no details on sterilisation procedures, and there was no suggestion that the prefilled plastic syringe which it described had been subjected to terminal heat sterilisation. Aseptic filling was therefore the method used in (12) for producing the syringe.

The Opposition Division had wrongly applied the teaching of citation (5), which related to "static systems", to syringes which represented a "dynamic system". A syringe would not be perceived by a skilled person as being a container within the meaning contemplated in (5). Plastic vials, jars etc. referred to in (5) were static containers in the sense that the container was closed by a static cup or bung which was held firmly in place by suitable means. The prefilled syringe of the present invention had a slidable piston and was accordingly a dynamic system, which was a far more complicated system than a static bottle. The use of counterpressure in the autoclaves of (5) would possibly prevent gross deformations of a plastic syringe and reduce relative movement of the piston in

the syringe during autoclaving. However, there was nothing in (5) to suggest that plastic articles would not suffer the normal deformation and shrinkage as a result of heat alone. While such deformation and shrinkage would not have been perceived by the skilled person to cause a problem with static containers, the problem with plastic syringes was not the relative movement of the piston in the syringe barrel during autoclaving, but whether or not the piston would slide in the barrel to maintain a sterile seal after sterilisation was complete.

The arguments and conclusions mentioned above in respect of (5) held true in every aspect for the state of the art according to citation (9a), relied on by the Respondents for the first time in the appeal proceedings.

In addition to the perceived technical problems, the long-standing use of non-heat sterilisation methods for sterilising plastic syringes and the fact that the autoclaves of the type disclosed in (5) and (9a), although known since 1981 and 1972, respectively, were never used for autoclaving prefilled syringes, established a prejudice in the art against using heat-sterilisation for sterilising prefilled plastic syringes. The affidavits of Gerlof Homan provided adequate evidence of the existence of such prejudice.

The inventiveness of the claimed process was moreover supported by the fact that in the medical field, too, there was a long-standing, well recognised need for a solution which existed in connection with the use of aseptically filled plastic syringes and prefilled glass

syringes. The evidence of the commercial success of prefilled plastic syringes which was directly attributable to the features of the invention was a further strong indication of an inventive step in the present case.

VII. The submissions of the Respondents 02 in support of their requests, both in the written procedure and at the oral proceedings, can essentially be summarised as follows:

It could not be ignored that at the priority date of the contested patent the following embodiments had already been made available to the public in the state of the art pertaining to prefilled glass and plastic syringes, on the one hand, and to heat- sterilisation of plastic materials as such and liquids contained in different kind of plastic containers by autoclaving, on the other:

- aseptically filled, sterile plastic syringes containing liquid materials, for example, contrast media suitable for injection, see citation (12);

- prefilled sterile glass syringes which were subjected to terminal sterilisation by autoclaving, see (1);

- use of counterpressure to avoid relative movement of the piston in the syringe barrel during autoclaving of the syringe, see citation (1);

- plastic materials which were susceptible to autoclaving at temperatures up to 160°C without suffering any shrinkage or deformation, see citation (9a);

- use of counterpressure for the sterilisation of liquids and solutions contained in sealed plastic containers, such as bottles, vials, jars and so on, to avoid problems of deformation or sealing due to the overpressure of the liquids or solutions developed during autoclaving, see citations (9a), (5).

On the basis of the state of the art referred to above, either citation (1) or citation (12) could be considered as the closest state of the art. Taking into account that all claims of the contested patent related to a method for producing prefilled, sterile plastic syringes, citation (12), which was already concerned with sterile prefilled plastic syringes, should possibly be given preference as the closest state of the art over (1). Moreover, (12) already pointed clearly to the considerable benefits and advantages of prefilled syringes made from plastic over glass prefilled syringes. The technical problem could therefore be seen as that of providing another, potentially improved method for producing sterile prefilled plastic syringes.

The skilled person seeking in the state of the art a solution to this problem which avoided the steps of aseptically assembling and filling the syringe and ensured an increased sterility assurance level would necessarily have come upon the method disclosed in (1) for the manufacture of a sterile prefilled glass syringe, including the step of terminally autoclaving the syringe together with its contents. As this teaching given in (1) was virtually the only reasonable alternative derivable from the state of the art to aseptic filling processes, the skilled person faced

with the stated technical problem would have found himself in a "one-way street" situation leading him to apply the teaching of (1) to the manufacture and sterilisation of prefilled plastic syringes as well.

The Appellants had repeatedly asserted that the perceived acute difficulties and technical problems the skilled person would have been confronted with, when applying the sterilisation method disclosed in (1) to prefilled plastic syringes, would in reality centre on the maintenance of the sterility of the seal and the slidability of the piston in the barrel during autoclaving. In spite of these allegedly insurmountable problems and difficulties associated with the terminal heat-sterilisation of plastic syringes, the skilled person was given in the contested patent extremely short instructions how to deal with them. In fact the instructions in the contested patent were limited to the suggestion of using a syringe barrel made from a suitable polymer such as polypropylene or a co-polymer of polypropylene and polyethylene and a piston of the desired shape made from a suitable elastomeric plastic or rubber material (see column 2, line 58 to column 3, line 6), and autoclaving the prefilled syringe at a temperature in the range of 120°C to 125°C (claim 3).

The specialist, endowed with the high level of skill enabling him to reduce the above-mentioned, rather rudimentary teaching of the contested patent to practice by selecting suitable materials for the syringe barrel and the piston and appropriate conditions to be applied during autoclaving of the prefilled syringe, would have known from (9a) of the existence of certain types of plastic materials with extremely good form-retaining properties, such as polycarbonate or polymethylpentene which could be sterilised at temperatures up to 140°C and 160°C, respectively, without any precautions.

He would also have learned from (9a) that polypropylene, high density polyethylene and thermosetting plastic materials could generally be autoclaved at a temperature of 121°C and that the problem of shrinkage and deformation of filled and sealed plastic containers of any shape could successfully be avoided by appropriately compensating the overpressure of the liquid generated during autoclaving in the plastic container.

In addition, the skilled person could easily find in a standard textbook the coefficients of thermal expansion of the different plastic and rubber materials and had thus the possibility of selecting for the syringe barrel, on the one hand, and for the piston, on the other, suitable materials having the same or at least a similar degree of thermal expansion within the required temperature range. The alleged problem of maintaining the sterility of the seal and the slidability of the piston in the barrel during autoclaving did therefore in reality not arise.

Moreover, as could be seen, for example, from Figure 3 in (12), at the priority date of the patent it was already common practice to use a plunger or piston, having a series of sealing flanges to reduce the contact area between the piston head and the inside surface of the barrel and to eliminate any possible risk of deformation caused by the expansion of the piston head.

Thus, starting from (12) as the closest prior art, the subject-matter of the contested patent was obvious to a person skilled in the art from a combination of the teachings of citations (1) and (9a) and his common general knowledge.

VIII. Respondents 01 agreed in every aspect with the arguments and submissions produced by Respondents 02 in the course of the appeal proceedings.

IX. As their main request, the Appellants requested that the decision under appeal be set aside and the patent be maintained unamended;

as their first auxiliary request, they requested that the patent be maintained in amended form on the basis of an amended claim 1, including the feature of dependent claim 2 as granted, followed by claims 3 and 4 as granted, to be renumbered as dependent claims 2 and 3;

as their secondary auxiliary request, they requested that the patent be maintained in amended form by adding in claim 1 of the main request following the feature "filling the barrel (22) through its open end (28) with a desired quantity of a liquid material" the words "suitable for injection";

as their third auxiliary request, they requested that the patent be maintained in amended form by adding in claim 1 of the first auxiliary request following the feature "filling the barrel (22) through its open end (28) with a desired quantity of a liquid contrast media" the words "suitable for injection".

X. Both Respondents 01 and Respondents 02 requested that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

2. *Determination of the closest prior art*

2.1 For an objective assessment of the technical problem to be solved, it is established legal practice in the EPO to determine the closest prior art to the claimed invention. In the present case it has to be decided whether the disclosure of citation (12) or citation (1) comes closer to the subject-matter of the contested patent.

As has repeatedly been acknowledged in the Appellants' submissions (see especially statement of grounds of appeal, page 6, point 12 and page 8, point 17; letter dated 25 May 1995, page 1, point 2) and in the submissions of Respondents 02 as well (see letter dated 30 June 1998, page 6, point 2.7) and has, moreover, been approved by all parties during oral proceedings before the Board, at the priority date of the contested patent prefilled sterile plastic syringes were indeed known in the state of the art. It was also not disputed that in all cases such prefilled sterile plastic syringes were produced in conventional manner by separately sterilising the syringes an their contents and subsequently filling and sealing the syringes under aseptic conditions.

Document (12) was cited during the appeal proceedings as illustrative of this state of the art. This citation discloses prefilled plastic syringes which contain the desired injection fluid, for example a contrast

material for radiographic examinations, stored in the cylindrical body of the syringe in sterile conditions and ready to be used (see the whole document, especially column 1, lines 6 to 11, 63 to 66, column 3, lines 9 to 13).

On the other hand, citation (1) is essentially concerned with an industrial process for producing prefilled sterile glass syringes including their terminal sterilisation by subjecting the assembled and sealed syringes together with their contents to autoclaving, while maintaining an appropriate counterpressure in the sterilisation zone.

2.2 Although the claimed invention relates to an improved process for producing a known medical device, namely a syringe, rather than to a process for preparing a known chemical compound, the Board considers it nevertheless appropriate in connection with the determination of the closest prior art in the present case to refer to Decision T 641/84 of 24 September 1991. In the said decision (see especially Reasons, point 3) the Board of Appeal concluded that in cases where the invention related to the improvement of a manufacturing process for known chemical compound, the only documents to be considered when determining the closest prior art were those which described that compound and its production. Only through comparison with these documents could a skilled person determine whether an improvement in the production of the target compound had been achieved, and hence whether they would have to be taken into consideration in formulating the problem to be solved by the invention.

2.3 As has been pointed out in Decision T 254/86 (OJ EPO, 1989, 115, see especially Reasons, point 15) another decisive criterion which is frequently applied to the determination of the objectively closest state of the

art in cases where a claimed invention is attacked on the basis of more than one piece of prior art belonging to the same technical field, is the choice of the closest starting point, i.e. the prior art from which the claimed invention could most easily have been made by a skilled person at the filing date of the patent.

2.4 Having compared, in the light of the principles and considerations set forth above, the patent's subject-matter with the relevant state of the art available in the proceedings, in particular citations (1) and (12), the Board concurs with the Respondents' submissions during oral proceedings that the prior art relating to prefilled sterile plastic syringes and the conventional method of their manufacture, as referred to in point 2.2 above in connection with document (12), comes closer to the claimed invention than the disclosure of citation (1) relating to prefilled sterile glass syringes and a manufacturing process therefor, notwithstanding that the manufacturing process of (1) already includes the step of terminally autoclaving the syringe together with its contents and that (1) was therefore deemed to be the closest state of the art in the decision of the first instance and also by the Appellants during oral proceedings. To complete the picture, it should however be noted that citation (12) was not available as state of the art in the first instance opposition proceedings.

The Board's decision to start from (12) as the closest prior art to the invention is primarily based on the following considerations:

First, the Board sees no sound reasons why the principles and conclusions laid down in Decision T 641/89 (vide supra) should be valid only for manufacturing processes for chemical compounds and should not equally hold true for the present case, even

if one takes into account that the present invention relates to the improvement of a manufacturing process for prefilled plastic syringes. In the Board's view, it appears nevertheless reasonable to follow the reasoning behind the cited decision and to apply it *mutatis mutandis* to the present case.

In this connection it should once more be emphasised that the contested patent exclusively contains process claims , thus taking into account that the products of the claimed process, i. e. the syringes themselves, were known per se. It appears therefore appropriate in the present case to start from the known product and the conventional method of its manufacture [see point 2.2 above in connection with document (12)] as the closest state of the art to the invention, rather than from (1) relating to a process for producing a different product, that is to say prefilled sterile glass syringes, even if the process for producing the latter is in respect of its technical features related to the process of the invention.

As a further point it should be noted that the need for prefilled sterile plastic syringes for certain purposes was clearly recognised and was within certain limits adequately satisfied by the inventors of document (12) (see especially column 1, lines 11 to 23). Prefilled syringes made from plastic represent in view of their increased physical stability, their lower costs and their suitability for large volume injections in general a considerable step forward over glass syringes. The remaining task was to improve the process for their manufacture. Therefore, the skilled person seeking to develop the conventional method for the manufacture of prefilled plastic syringes in a certain direction had in the Board's opinion no valid reason to return to glass syringes as a starting point for his

invention, since by doing so he would fall behind a considerable technical progress already achieved in the field of prefilled syringes. Taking this into account, the most promising starting point to the invention available to the skilled person was, in the Board's judgment, the prior art relating to prefilled sterile plastic syringes and the conventional method of their manufacture, as referred to in point 2.2 above in connection with document (12).

Such an approach is in line with the normal development work of a person skilled in the art who normally starts from such a specific embodiment, in the present case from a specific process of producing prefilled sterile plastic syringes, and who tries to adapt, to modify or to improve that existing embodiment, in order to solve the technical problem arising.

3. *The Problem and the Solution*

3.1 Although the known prefilled sterile plastic syringes already overcome certain disadvantages associated with the prior art glass prefilled syringes, such as the relative fragility, the unsuitability for large volume injections and the relatively high production costs of the latter, the conventional process of producing said plastic syringes requiring the step of filling the syringes under aseptic conditions is time-consuming and rather expensive. More importantly, as has been pointed out by the Appellants during the oral proceedings, the current aseptic filling processes, even if performed under optimal conditions, can be validated to ensure a sterility assurance level (SAL) of the order of 10^{-3}, which is considered insufficient to ensure attenuation of certain viruses. For comparison, the terminal

sterilisation method, if properly conducted and validated, will achieve a 10^{-6} SAL (see in this respect also R. Murty, Aseptic Processing - A Retrospective Review in Pharmaceutical Technology, 15th Anniversary. 1988, 24-30).

Thus, in the light of the closest state of the art, the technical problem the invention sets out to solve may be seen as that of improving the process of producing sterile prefilled plastic syringes with the particular aim of achieving a significantly higher level of sterility assurance without impairing their function as a syringe and without compromising their sterility during the required shelf life. From a medical and ethical point of view, the improvement of the sterility assurance level is undoubtedly a prevailing and important objective in the manufacture of pharmaceutical products, in particular, injectable preparations, in order to assure that they are free of infection hazards.

3.2 In claim 1 of the contested patent the Appellants suggest solving this problem by a method of producing prefilled plastic syringes which involves a series of sequential operations required for cleaning, assembling, filling and sealing the syringe, and, what is crucial to the solution of the stated problem, the step of terminally autoclaving the assembled and sealed syringe to sterilise the plastic syringe and its contents, while maintaining a pressure on the outside surfaces of the syringe at least equal to the pressure of the syringe contents during autoclaving.

In view of the fact that the terminal sterilisation method in connection with autoclaving is well recognised in the art to ensure a significantly higher sterility assurance level than that achieved by aseptic filling processes (see point 3.1 above) and, moreover,

in the absence of any convincing arguments or any evidence to the effect that terminal sterilisation of prefilled plastic syringes by autoclaving under the specific prerequisites and conditions of the claimed process would possibly impair their function as a syringe with a dynamic sterile seal for the required shelf life, the Board is satisfied that the solution of the stated problem has been achieved by making available the manufacturing process of the contested patent.

4. *Novelty*

The novelty of the subject-matter of the contested patent has already been acknowledged in the decision of the Opposition Division. Since none of the cited documents discloses a method of producing a prefilled, sterile plastic syringe including the step of terminally autoclaving the assembled and sealed syringe to sterilise the syringe and its contents, the Board sees no reason to call the novelty into question. Furthermore, the question of novelty was not at issue during oral proceedings before the Board.

5. *Inventive Step*

5.1 The invention is defined in claim 1 as a multi-stage process which involves a series of subsequential steps required for cleaning, assembling, filling and sealing the syringe (see steps (a) to (g) in paragraph I above) and the final step of autoclaving the assembled and sealed syringe to sterilise the plastic syringe and its contents (step (h) in paragraph I above).

A complete multi-stage process may be inventive by virtue of the combination alone of the individual stages, without there being any patentable individual

stages. On the other hand, the inventive character of the whole process may be based on at least one inventive part (see in this respect Decision T 163/84, OJ EPO, 1987, 301, Reasons, point 7).

In the present case, the Appellants themselves have never claimed that any of the procedural steps (a) to (g) taken individually was inventive. This is also the opinion of the Board. Having regard to the disclosure of citation (1), the series of procedural steps (a) to (g) in claim 1 of the contested patent merely appears to reflect the ordinary sequential operations which are routinely carried out in the manufacture of syringe ampoules or ready to use syringes, irrespective of the particular material the syringes are made from, i.e. glass or plastic.

In particular, the steps (a) and (b) of the claimed process are derivable for a person skilled in the art from citation (1), page 5, lines 57 to 59; step (c) is derivable from citation (1), page 5, lines 30 to 34; step (d) is derivable from citation (1), page 5, lines 34 to 40; steps (e), (f) and (g) are derivable from citation (1), page 5, lines 61 to 69.

5.2 Thus, the relevant question to be decided in the present case under Article 56 EPC is, in the Board's judgment, whether the skilled person, faced with the stated technical problem and guided by his common general knowledge and his familiarity with the relevant state of the art and also with related art, would have considered and chosen also step (h) of the process in (1), viz. autoclaving the assembled and sealed syringe and its contents under proper counterpressure, as a practicable method for the sterilisation of prefilled plastic syringes, in the reasonable expectation of solving the stated problem and making the desired improvement available.

5.3 It should be noted that the skilled person could have taken, in principle, a number of possibilities into consideration in order to solve the problem associated with the sterilisation of prefilled plastic syringes. As can be seen, inter alia, from the introductory part of the present patent specification, a certain number of different methods of producing sterile syringes, including plastic syringes, have already been envisaged in the state of the art (cf. column 1 lines 10 to 33).

It was, moreover, common specialist knowledge that, for example, dry heat sterilisation or non-heating methods, such as sterilisation with gases, sterilisation by radiation with either electromagnetic radiation or particulate radiation, or sterilisation by filtration, are reliable alternatives to the sterilisation with moist heat in the form of saturated steam under pressure (autoclaving) used in the contested patent.

In view of the above considerations, the Board is unable to follow the argument relied on by the Respondents in the oral proceedings that the skilled person seeking a solution to the problem posed would have found himself in the present case in a so-called "one-way street" situation. In the Board's judgment, the present case does not belong to the extremely exceptional cases where the skilled person was confronted with a total lack of alternatives to the only possible option which presented itself as the solution of the respective technical problem, as was the case e.g. in Decision T 192/82 (OJ EPO 9/1984, 415; "one-way street" situation).

5.4 Although the skilled person was thus free in choosing a suitable sterilisation method, the relevant state of the art submitted in the proceedings in conjunction with his common general knowledge nevertheless provided him, in the Board's opinion, with a strong incentive to

think of improving the sterility assurance level by the method which proved already in (1) to be very effective, i.e by subjecting the syringe and its contents to terminal sterilisation by autoclaving.

First, the skilled person seeking to increase the sterility assurance level of the prefilled syringe would give priority to the most effective and most promising sterilisation method available in the state of the art. In doing so , he would take account of the fact that terminal sterilisation was generally known to be far superior to any aseptic filling process (see point 3.1 above). Moreover, notwithstanding that a certain number of different sterilisation techniques were available (see point 5.3 above), it was agreed by all parties that autoclaving, given sufficient heat-resistance of the substrate to be sterilised to withstand heat sterilisation, was commonly known in the art to be the most dependable and widely used method for the destruction of all forms of microorganisms (see in this respect as one example only of standard textbooks on the theory and practice of the pharmaceutical sciences representing the common general knowledge in this field: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton Pa., 1980, 1391-1393).

5.5 Furthermore, the skilled person, who had already in view of the above-mentioned advantages and benefits sound reasons to take terminal autoclaving into consideration as possibly being the most favourable solution to the stated problem, would have been strongly confirmed in his initial considerations by the prior art of (1). Thus, citation (1) not only suggests that terminal sterilisation of prefilled plastic syringes by autoclaving would indeed be highly desirable and effective but provides also clear evidence that this sterilisation method was in the case

of prefilled syringes made from glass in fact practicable without compromising the sterility of the sliding seal or causing the piston head made from plastic or rubber to malfunction, in spite of the expected thermal expansion of the piston during autoclaving, if a certain type of autoclave is used which is appropriately designed and equipped to regulate the temperature and to maintain the pressure on the outside surfaces of the syringe or syringe ampoule at least equal to the pressure of the syringe contents during autoclaving (see (1), page 6, left hand column, line 10 from the bottom to right hand column, penultimate paragraph).

5.6 In the effort to find an answer in the prior art to the question whether the particular sterilisation method disclosed in (1) would be similarly applicable to prefilled plastic syringes, the skilled person would have considered the teaching of document (9a), which describes an autoclave steriliser of the type used in (1) and its wide application to the sterilisation of infusion and injection liquids in both glass bottles and plastic containers.

The present claims refer to the manufacture of syringes made from plastic in general. With the exception of a possibly functional limitation requiring that the material used be suitable for producing a syringe, they contain no further limitation as to the plastic material to be used. In view of the breadth of the claims in this respect, the Respondents' argument is correct that citation (9a) provides a straightforward solution to the stated problem, insofar as in connection with autoclaving (9a) refers to certain plastic materials, more specifically polycarbonate and polymethylpentene, which would, in view of their relevant glass-like physical properties with respect to heat-resistance and form-retaining, immediately be

suitable for supplanting of glass by plastic in the manufacture of prefilled syringes, including the step of terminal sterilisation, of the filled and sealed plastic syringe by autoclaving without any particular precautions (see (9a), page 9, left hand column, penultimate paragraph to right hand column, end of first paragraph).

5.7 In the description of the contested patent (see column 3, lines 2 to 4) reference is made to the use of polypropylene or a co-polymer of polypropylene and polyethylene as the appropriate plastic materials for the syringe barrel. Even if this suggestion in the contested patent is followed and the above-mentioned materials are used, citation (9a) directs the skilled person clearly to the possibility of sterilising filled and sealed plastic containers made from polypropylene and polyethylene by subjecting them to autoclaving. More specifically, containers made of polypropylene are reported in (9a) to be sterilisable with sufficient counterpressure at temperatures in excess of 120°C, containers made of high density polyethylene under sufficient overpressure up to approximately 118°C and containers made of high density/low density polethylene composites under sufficient overpressure up to approximately 110°C (see page 9, right hand column, line 6 to page 10, right hand column, end of first full paragraph).

Notwithstanding this, the Appellants have consistently argued that the Respondents and the Opposition Division in its decision had ignored the very significant differences between what they call "static systems", such as sealed plastic bottles, plastic jars or other plastic containers, which are subjected to autoclaving in citation (9a) and (5) and a syringe, called a "dynamic system". They argued further that, in spite of the counterpressure applied during sterilisation, the

effect of heat alone on plastic was to cause it to soften or shrink. On the other hand, the effect of heat on the conventional rubber piston would have been such as to cause extension. Thus, according to the Appellants' allegation, the crucial problem and real challenge, which the skilled person had in reality to overcome in autoclaving a prefilled plastic syringe, and with which the prior art of (9a) and (5) was not confronted at all, was maintaining a sterile sliding seal between the piston head which was conventionally made of rubber and the inside surface of the plastic barrel of the syringe without compromising the sterility of the seal and the functioning of the piston.

In spite of these alleged difficulties and problems, the skilled person is given in the contested patent only very short and general instructions on how to deal with them. Such instructions are limited to the advise to the skilled person to choose a suitable polymer for the syringe barrel and a suitable elastomeric material or rubber material for the piston (see line 68 in column 2 to line 7 in column 3):

"The syringe barrel is produced by a suitable plastic-forming process such as injection molding of a suitable polymer such as polypropylene or a co-polymer of polypropylene and polyethylene. The tip seal and the piston are likewise produced by injection molding a suitable elastomeric material or rubber material to the desired shapes". The preferred conditions for autoclaving are briefly stated in claim 3: "autoclaving by heating the assembled and sealed syringe is performed by heating the assembled and sealed syringe to a temperature in the range of 120°C and 125°C to reach an Fo of approximately 20.

5.8 The Board adopts the view expressed in Decision T 60/89 (OJ EPO 6/1992, 268, see especially Reasons, point 3.2.5) that the same level of skill has to be applied when, for the same invention, the two questions of sufficient disclosure and inventive step have to be considered. Hence, if one accepts in the present case in favour of the Appellants that the above disclosure in the contested patent is enabling within the meaning of Article 83 EPC, then the inevitable conclusion must be drawn that, in the Appellants' own judgment, the skilled person, who is here to be seen as a graduate specialist or a team of specialists of that skill being familiar with all kind of sterilisation and autoclaving techniques and being also familiar with the properties and behaviour of all kinds of plastic and natural or synthetic rubber materials under the influence of heat and pressure, knew at the priority date of the contested patent or was at least able to find out without undue burden what kind and combination of materials would have the desired properties and capabilities to withstand autoclaving under appropriate conditions, such as counterpressure and temperature, without compromising the sterility of the sliding seal of the plastic syringe and without impairing the functioning of the piston.

The specialist endowed with the high level of skill mentioned above would indeed have known that autoclaves exist which are specifically designed and equipped to provide the exact degree of overpressure and temperature in the sterilising zone to ensure that plastic containers made from polypropylene or appropriate types of polyethylene retain their original shape and to ensure that excessive strain on the material is eliminated (see (9a), page 9, left hand column, third paragraph, lines 3 to 8). From this he would reasonably have concluded that the syringe barrel similarly maintains its original shape during

autoclaving and that therefore, contrary to the Appellants' assertion in this respect, a certain analogy can justifiably be drawn between the behaviour of a sealed plastic bottle and a sealed plastic syringe during autoclaving in this particular type of autoclave.

Moreover, in seeking suitable, commercially available materials for the syringe barrel, on the one hand, and the piston, on the other, the specialist mentioned above would preferably have searched for and selected materials which have about the same or at least a similar thermal expansion coefficient. During the oral proceedings, the Respondents have provided, in the Board's judgment, convincing arguments that, in doing so, the skilled person would easily have found in a standard textbook, for example, that both polypropylene as the material for the syringe barrel and natural rubber as the material for the piston head would suffer the same thermal expansion of ca. 3 Vol.%, or chlorobutyl rubber a thermal expansion of ca. 4.5 Vol.%, within the crucial temperature range of from 21 to 121°C. Since at the priority date of the contested patent the skilled person could select for the syringe barrel and the piston suitable materials having about the same degree a thermal expansion, the alleged problem that the expansion of the rubber piston head would cause it to press against the walls of the plastic syringe resulting in a deformation of the syringe, and the problem of maintaining the sterility of the seal and the slidability of the piston in the barrel during autoclaving could therefore also easily be eliminated by choosing suitable materials.

The Respondents' argument is in the Board's opinion also convincing that it was at the priority date of the patent already common practice - see citation (12)- to use as the seal for the syringe a plunger or piston

head having a series of sealing flanges to reduce the contact area between the piston head and the inside surface of the barrel in order to eliminate any possible risk of deformation caused by the expansion of the piston head during autoclaving.

In conclusion, in the present case the skilled person endowed with the skills mentioned above was provided with a clear indication from the prior art of (9a) and his common general knowledge directing him clearly to the possibility of applying the sterilisation method used in (1) to prefilled plastic syringes, as well with the reasonable expectation of solving the technical problem without undue burden. The necessity of experimentally confirming a reasonably expected result does not render an invention non-obvious. Hence, step (h) of the claimed process was similarly obvious to a person skilled in the art.

5.9 Apart from the fact that in view of the foregoing none of the steps (a) to (h) taken individually was found to be inventive, there is no doubt that the complete process is also not inventive as a combination of the individual steps. Citation (1) discloses a process involving essentially the same combination of sequential steps for producing a sterile prefilled syringe (see point 5.1 supra). Although the sequence of the individual steps is slightly modified in present claim 1 as compared with the prior art of (1), such modification was merely a matter of routine for the skilled practitioner and therefore cannot contribute to the acknowledgment of an inventive step in the absence of any unexpected advantages or effects associated with the said modification.

5.10 The Appellants have further argued that a prejudice against subjecting prefilled plastic syringes to autoclaving had existed. However, a prejudice in a

particular field relates to an opinion or preconceived idea widely or universally held by experts in that field. Since, contrary to the requirements set forth above, the existence of such prejudice has not adequately been demonstrated, e.g. by reference to literature or encyclopaedias published before the priority date, it cannot be accepted as an indication of an inventive step.

The Board has duly taken account of the affidavits of Gerlof Homan. In this respect the Appellants' attention is drawn to the fact that in order to claim that a prejudice has indeed been overcome, the proposed solution has to go beyond the prevailing conventional teaching by contradicting the experiences and ideas in the field. It is not enough to adduce the negative opinion of individual experts, as it is here the case with the affidavits submitted in the appeal proceedings (see in this respect e.g. Decisions T 62/82 dated 23 June 1983, especially Reasons, point 5.6; T 943/92 dated 10 April 1995, especially Reasons, point 7.1).

5.11 The Board does not question that syringes produced according to the invention possibly may have become a commercial success. However, in view of the fact that the technically relevant examination of the inventiveness of the claimed manufacturing process led to a clear negative result, such possible commercial success is insufficient for the acknowledgment of an inventive step in the present case (see in this respect Decisions T 219/90 dated 8 May 1991, especially Reasons, point 6; T 5/91 dated 24 June 1993).

The fact that prefilled sterile plastic syringes were known from (12), disproves the Appellants' submissions that the alleged long-felt want for such syringes did in fact exist.

6. *Auxiliary Requests*

6.1 According to the first auxiliary request, claim 1 is restricted to a method of producing a sterile plastic syringe prefilled with a liquid contrast media. Step (f) of the claimed process according to the first auxiliary request reads accordingly as follows: (f) "filling the barrel through its open end with a desired quantity of a liquid contrast media". The particular advantages and principal applications of prefilled plastic syringes for the injection of contrast material during radiographic examinations, preferably in combination with an automatic power injection apparatus, are already disclosed in (12), see especially column 3, lines 9 to 18). Since also no convincing arguments or evidence have been provided that in the terminal heat-sterilisation of contrast media the skilled person was confronted with specific problems which were significantly different from those experienced in the terminal heat sterilisation of other conventional liquid injectable preparations for injection into blood vessels, in the Board's judgment, the subject-matter of claim 1 of the auxiliary request does not involve an inventive step.

6.2 Step (f) of the claimed process according to the second auxiliary request reads as follows: (f) "filling the barrel through its open end with a desired quantity of a liquid material suitable for injection".

Step (f) of the claimed process according to the third auxiliary request reads as follows: (f) "filling the barrel through its open end with a desired quantity of a liquid contrast media suitable for injection."

It appears clear that the addition "suitable for injection" in step (f) in the second and third auxiliary request cannot contribute to the acknowledgment of an inventive step in the present case because all the observations and arguments in this decision take already into account that the contents of the prefilled sterile plastic syringe according to the invention are suitable for injection.

Moreover, the Appellants have clearly indicated during oral proceedings that the second and third auxiliary request were primarily filed in response to the alleged prior use according to (11) submitted by the Respondents during appeal proceedings.

In the present case, the Board was able to come to the decision without the requirement of deciding on the admissibility of (11) into the proceedings.

7. In conclusion, none of the requests was found to be acceptable under the terms of Article 52(1) in conjunction with Article 56 EPC.

8. *Sufficiency of disclosure*

The Respondents' arguments on the grounds of insufficiency under Article 100(b) in conjunction with Article 83 EPC were already dealt with in point 5.8 above in connection with inventive step and by reference to Decision T 60/89 (loc. cit.). Since the appeal has to be dismissed and the patent remains revoked for lack of inventive step, insufficiency as a ground for opposition is no longer of relevance to the present case.

Order

For these reasons it is decided that:

The appeal is dismissed

The Registrar:

P. Martorana

The Chairman:

P. Lançon