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# D E C I S I O N
# of 31 May 2005

**Case Number:** T 0779/04 - 3.2.5

**Application Number:** 94928996.1

**Publication Number:** 0680401

**IPC:** B29C 45/17

**Language of the proceedings:** EN

**Title of invention:**
Method for the preparation of pre-filled plastic syringes

**Patentee:**
BRACCO International B.V.

**Opponent:**
Schering AG

**Headword:**
-

**Relevant legal provisions:**
EPC Art. 54, 56, 83, 123

**Keyword:**
"Extension beyond the content of the application as filed (no)"
"Sufficiency of disclosure (yes)"
"Novelty (yes)"
"Inventive step (yes)"

**Decisions cited:**
-

**Catchword:**
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**Case Number:** T 0779/04 - 3.2.5

# D E C I S I O N
**of the Technical Board of Appeal 3.2.5**
**of 31 May 2005**

**Appellant:** (Proprietor of the patent)
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**Decision under appeal:**
**Decision of the Opposition Division of the European Patent Office posted 30 April 2004 revoking European patent No. 0680401 pursuant to Article 102(1) EPC.**

**Composition of the Board:**

**Chairman:** W. Moser
**Members:** W. R. Zellhuber
W. Widmeier

## Summary of Facts and Submissions

I. The appellant (patent proprietor) lodged an appeal against the decision of the Opposition Division revoking the European patent No. 0 680 401.

II. An opposition was filed against the patent in suit as a whole and based on Articles 100(a) EPC (lack of novelty, Article 54 EPC, and lack of inventive step, Article 56 EPC), 100(b) EPC and 100(c) EPC. The Opposition Division held that the ground for opposition under Article 100(a) (lack of inventive step, Article 56 EPC) prejudiced the maintenance of the patent in suit having regard to the cited documents.

III. Oral proceedings were held before the Board of Appeal on 31 May 2005.

IV. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the following documents filed on 29 April 2005:

(i) claims 1 to 7 as main request; or

(ii) claims 1 to 7 as first auxiliary request; or

(iii) claims 1 to 6 as second auxiliary request; or

(iv) claims 1 to 7 as third auxiliary request.

As a fourth auxiliary request, the appellant requested that the decision under appeal be set aside and that the patent be maintained as granted.

The respondent (opponent) requested that the appeal be dismissed.

V. Claim 1 according to the main request reads as follows:

"1. A method for making prefilled plastic syringes under conditions substantially free of pyrogen and viable and non-viable particulates, the said syringes including as components a barrel (1) with a nozzle (2) and an open end (4) opposite said nozzle, a nozzle tip seal (3), and a piston (5) sliding in the barrel, said method comprising
(a) molding suitable plastics into syringe components(1, 3, 5);
(b) attaching tip seal (3) to nozzle (2);
(c) filling the barrel (1) with injectable diagnostically or medically suitable material;
(d) assembling piston (5) in said open end (4) of the barrel, characterized in that
(e) in step (a) at least one of said components (1, 3, 5) is molded under class 100 conditions (SI = M 3.5) or better in regard to viable and non-viable particulates, and under Class MCB-3 conditions or better in regard to viable particulates, and wherein the level of gram negative microorganisms is less than 35.3 cfu/$m^3$ (1 cfu/$ft^3$)."

VI. The following documents are referred to in the present decision:

D3: G. Galic and S. Maus, "Molded Parts Discharged without Opening the Mold", ANTEC '91, pages 412 to 416;

D6: US-A 4,718,463;

D7: US-A 4,880,581;

D8: H. Eckardt, "Clean-room Injection Moulding", plast europe, March 1992, pages 54 and 55, Carl Hanser Verlag, Munich;

D9: Pharmacopeial Forum, Volume 18, Number 5, pages 4048 to 4054, Sept.-Oct. 1992, "<1116> MICROBIOLOGICAL EVALUATION AND CLASSIFICATION OF CLEAN ROOMS AND CLEAN ZONES";

D10: Federal Standard 209E, "Airborne Particulate Cleanliness Classes in Cleanrooms an Clean Zones", revised 1992 by the Institute of Environmental Sciences, pages i to vi and 1 to 48;

D11: Commission of the European Communities, Directorate-General for Internal Market and Industrial Affairs, "The Rules governing Medicinal Products in the European Community", Volume IV, "Guide to Good Manufacturing for Medicinal Products", pages 1 to 86, January 1989;

D13: WO-A 90/14204;

D15: Second Declaration of Gayle Heffernan, dated 29 April 2005;

D19: WO-A 89/07462.

VII. In the written procedure and during oral proceedings, the appellant argued essentially as follows:

*Sufficiency of disclosure*

The respondent failed to point to any serious doubts, substantiated by verifiable facts, that would justify a finding of insufficiency of disclosure.

Actually, documents D8 (cf. page 54, last paragraph) and D13 (cf. page 20, lines 25 to 28) showed that, at the priority date of the patent in suit, moulding under class 100 condition had been possible, even though it might have been difficult to achieve. Class MCB-3 condition constituted a standard, cf. document D9, page 4049, and, already for that reason, had to be regarded as a condition which could have been achieved at the priority date of the patent in suit. Furthermore, the patent in suit contained a specific teaching on this subject, cf. column 4, lines 22 to 29.

Maintaining all the conditions as set out in claim 1 of the main request allowed the production of syringe components under sufficient cleanliness and sterility.

*Novelty*

Document D19, cf. claim 18, made mention of moulding a cartridge barrel in an aseptic environment. However, there was no clear definition of the term "aseptic environment". In this respect, a plurality of different definitions could be found in the commonly available literature. In particular, as regards the total number of particles, the number of gram negative microorganisms or pyrogens, that term did not include any definition of any upper limits. Document D11 was a

guide for preparing, handling and filling medicinal products, rather than for making containers. It concerned a different subject and, thus, could not be used when it came to specifying the exact meaning of the term "injection moulding … in an aseptic environment" used in claim 18 of document D19.

The method according to claim 1 of the main request was thus novel.

*Inventive step*

The purpose of the method according to document D6 was the same as that of the patent in suit, namely to provide aseptic prefilled syringes. It referred to the problem of contamination with pyrogens, contrary to document D19. Document D6 thus represented the closest prior art.

The problem was to provide aseptic and clean prefilled syringes. It was solved by a method according to claim 1 of the main request, in particular, by a method for making components of a syringe under conditions substantially free of pyrogen and viable and non-viable particulates, wherein the cleanliness conditions which had to be met in step (a) ("molding suitable plastics into syringe components") of the method were defined. As a result, there was no need to wash the thus produced components with depyrogenated and thus expensive water.

When assessing inventive step, it had to be considered that, as regards cleanliness and sterility in the specific technical field of making medicinal products,

a person skilled in the art would not take any security risks. Furthermore, the specific problem coming up from contamination with pyrogens had to be considered. In fact, gram negative bacteria had a cell wall made primarily of lipopolysaccharide (LPS). If these bacteria were killed under antiseptic or sterilising conditions, fragments of the wall remained, and LPS, a pyrogen, would still cause an inflammatory response by the immune system. The resulting "shock" to the immune system could be serious or even fatal.

Document D6 suggested an elaborate water jet washing system for removing pyrogen. Document D6 thus did not hint at the solution suggested in the patent in suit.

Documents D3, D7 and D19 did not define what was meant by aseptic environment. Neither did they mention the problem arising from the presence of pyrogens. It had thus to be assumed that components produced according to any of the methods disclosed in documents D3, D7 or D19 had to undergo a depyrogenation process. These documents provided the raw material for the process disclosed in document D6. Moreover, document D19 concerned the production of syringes to be used by dentists for local treatments. The syringes were not intended to be used for systemic injections, and, thus, pyrogens were not a problem. A combination of any of the documents D3, D7 or D19 with the teaching of document D6 thus did not give rise to the method according to claim 1 of the main request.

Document D11 dealt with the preparation and handling of medicinal products with which syringes might be filled. Document D11 was not a guide for making the containers.

Accordingly, when making a container, a person skilled in the art would not consider applying the cleanliness levels described therein.

Consequently, the subject-matter of claim 1 of the main request involved an inventive step.

VIII. In the written procedure and during oral proceedings, the respondent argued essentially as follows:

*Sufficiency of disclosure*

The patent in suit did not disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In particular, it was silent about how the moulding should take place in order to fulfil the conditions set out in claim 1 of the main request. The class 100 condition was known to be difficult to achieve, and there was no solution disclosed as regards the mechanical problems. Furthermore, the patent in suit did not explain how to achieve an environment which was substantially free of pyrogens. The appellant itself submitted a document, cf. document D15, page 3, point 8, which confirmed that pyrogens passed through HEPA filters.

The MCB-3 class condition constituted a very low cleanliness level. Producing pharmaceutical products under that condition would not give rise to products which could be brought onto the market. The cleanliness level as set out in document D11 for the production of pharmaceutical products, i.e. Grade A, cf. the table on page 70 and page 72, point 6, of document D11, was far

more restrictive than that defined in claim 1 of the main request.

*Novelty*

The method of claim 1 of the main request was not novel with regard to the method disclosed in document D19. In particular, according to claim 18 of document D19, the barrel of the prefilled syringe was injection moulded in an aseptic environment. According to document D11, cf. page 72, preparing a medicinal product in an aseptic environment meant preparing under Grade A conditions, i.e. in an environment wherein the number of particles per $m^3$ having a size equal or above 0.5 µm did not exceed 3500, wherein the number of particles per $m^3$ having a size equal or above 5 µm was zero, and wherein the number of viable micro-organisms was less than 1 per $m^3$, cf. document D11, the table on page 70. Consequently, the class 100 condition (cf. definition in document D10, page 5, table 1) was thus met, the MCB-3 class condition far more than met, and, since, according to Grade A, the total number of viable particles was less than 1 particle per $m^3$, also the condition that the level of gram negative microorganisms was less than 35.3 cfu/$m^3$.

*Inventive step*

Assuming that the subject-matter of claim 1 of the main request was novel, it did not involve an inventive step. Document D6 was considered to represent the closest prior art. The problem was that the method for the purpose of depyrogenation, suggested in document D6, was very expensive. Accordingly, a person skilled in

the art would look for an improved and less cumbersome method for making prefilled syringes.

Document D7 suggested a specific solution, namely injection moulding of the barrel of the syringes in an aseptic and, due to HEPA-filters, particle free environment (cf. column 4, lines 3 to 21). Furthermore, due to the application of heat and pressure, contamination of the moulded components was *ab initio* avoided.

An aseptic environment required maintaining Grade A condition, cf. document D11, the table on page 70 and page 72, and, thus, class 100 conditions and, as regards viable particles, conditions which are far more restrictive than the MCB-3 class conditions claimed in claim 1 of the main request. Document D11 concerned the production of medicinal products, and prefilled syringes according to the patent in suit were medicinal products. A person skilled in the art would thus have considered the rules set out in that document.

A person skilled in the art would thus have replaced the costly and cumbersome washing steps according to document D6, by applying the method suggested in document D7, and would thus have arrived at the method according to claim 1 of the main request without inventive merit.

## Reasons for the Decision

1. *Allowability of the amendments (Article 123 EPC)*

The subject-matter of claim 1 is disclosed in the printed version of the application as filed in claims 1, 2, and 8 in connection with the passages on page 5, lines 5 to 27 and page 6, lines 15 to 17 of the description.

The subject-matter of dependent claims 2 to 7 is disclosed in claims 3, 4, 5, 9, 10 and 11, respectively, of the application as filed.

The description was amended to bring it into line with the subject-matter of claim 1 of the main request. The drawing corresponds to that of the application as filed.

In the Board's judgement, the amendments had been made in accordance with the requirements of Article 123(2) EPC.

Furthermore, the scope of protection conferred by independent claim 1 is more limited than that of claim 1 of the patent in suit as granted. The patent in suit as amended thus also meets the requirements of Article 123(3) EPC.

2. *Sufficiency of disclosure*

In the Board's judgement, the fact that achieving and maintaining the claimed conditions in a moulding process might be difficult is not an indication of

insufficiency of disclosure. The cleanliness levels like Class 100 and MCB-3 class constitute standards, cf. document D9, Table 1 on page 4053, and document D10, Table I on page 5. It has thus to be assumed that a person skilled in the art was enabled to carry out a moulding process, in particular, in an environment meeting these conditions. The patent in suit further indicates measures which might be taken in order to meet the conditions claimed in claim 1 of the main request, cf. column 4, lines 22 to 29 and column 4, line 47 to column 5, line 1. The question whether or not the final product can be brought on the market does not concern the question of sufficiency of disclosure.

To sum up, there is no evidence that a person skilled in the art, using common general knowledge, was not enabled to carry out the method for making prefilled syringes under the cleanliness conditions as defined in the claims according to the main request.

Therefore, the opposition ground as set out in Article 100(b) EPC does not prejudice the maintenance of the patent in suit as amended according to the main request.

3. *Novelty*

None of the cited documents discloses a method as claimed in claim 1 of the main request, including the step of moulding suitable plastics into syringe components (step (a)) under conditions as set out in feature (e) of the claim, i.e. class 100 conditions or better in regard to viable and non-viable particulates, Class MCB-3 conditions or better in regard to viable

particulates, and wherein the level of gram negative microorganisms is less than 35.3 cfu/$m^3$.

Document D19 discloses a method for making prefilled plastic syringes including the step of injection moulding of a component of the syringe (barrel) in an aseptic environment. However, document D19 does not define what is meant by aseptic environment, and it thus is not directly and unambiguously derivable from the disclosure of document D19 that "in an aseptic environment" means under the conditions as defined in feature (e) of claim 1 of the main request.

Document D11 is a "Guide to Good Manufacturing Practice for Medicinal Products", cf. cover page, and concerns the preparation, handling and filling of medicinal products. It is silent about making containers for medicinal products. Accordingly, the teachings under the heading "Aseptic preparations" on page 72, point 6 do not concern the step of moulding plastics into syringe components. They merely teach that handling of starting materials, preparation of solutions, and handling and filling of aseptically prepared products should be done in a Grade C and a Grade A zone, respectively. Moreover, from the definitions of "Grade A" and "Grade C" as indicated in the table on page 70 of document D11, it follows that Grade A, but not Grade C, is within the limits as set out in claim 1 of the main request.

Document D11 thus neither concerns the step of making containers, nor does it define the prerequisites for an environment to be an "aseptic environment". Consequently, it cannot be used as a specification of the "aseptic environment" under which the moulding step

is carried out according to the teaching of document D19.

It follows that the subject-matter of claim 1 of the main request is novel over the cited prior art.

4. *Inventive step*

4.1 Document D6, which represents the closest prior art, concerns a method of producing prefilled plastic syringes, wherein the plastic barrels are subjected to repeated water jet washing steps to remove contaminants and to depyrogenate the barrels. Subsequently, the assembled, filled and sealed syringes are subjected to autoclaving to sterilize them and their contents, cf. abstract and column 3, lines 13 to 20.

The object of the patent in suit is to provide an improved method of making clean and aseptic prefilled plastic syringes. It is achieved by a method according to claim 1 of the main request, in particular by a method for making prefilled plastic syringes under conditions substantially free of pyrogen and viable and non-viable particulates, wherein at least one of the components of the syringe is moulded under the three cleanliness conditions set out in claim 1 of the main request (Class 100, Class MCB-3, level of gram negative microorganisms). The claimed method allows "the preparation of a pre-filled plastic syringe in a less cumbersome and more efficient manner than known methods by obviating the need for subsequent treatments steps such as water washing", cf. column 2, lines 31 to 34 of the patent in suit.

4.2 Document D7 discloses a method for aseptic particle-free production of articles and suggests eliminating conventional sterilization steps by producing the blow moulded or injection moulded articles in an aseptic environment within a clean room, cf. column 1, lines 7 to 12 and 65 to 68, column 3, line 65 to column 4, line 2, and claim 1 of document D7.

However, document D7 does not explicitly define the conditions under which the articles are moulded, and, in particular, document D7 does not deal with the problem occurring from a contamination with pyrogens. It neither suggests making prefilled plastic syringes under conditions substantially free of pyrogens, nor does it indicate a limit with regard to the level of gram negative microorganisms, which are the main source for a contamination with pyrogens.

The same applies to documents D3 and D19, which suggest moulding of syringe components under class 100 conditions (document D3), or in an aseptic environment (document D19), but are silent about any limit as regards gram negative microorganisms, the pyrogen problem, and any measures to be taken in order to avoid pyrogens.

Consequently, a combination of the teaching of document D6 with the teaching of either of documents D3, D7 or D19 does not give rise to a method as claimed in claim 1 of the main request.

As mentioned above under point 3, document D11 does not concern a method for making containers and, consequently, does not teach any cleanliness levels

which have to be maintained when moulding plastics into syringe components. There is thus no hint for a person skilled in the art that moulding of syringe components under specific cleanliness conditions, in particular under the conditions as set out in claim 1 of the main request, would solve the problem underlying the patent in suit, i.e. rendering a depyrogenation step as disclosed in document D6 optional.

Therefore, the subject-matter of claim 1 of the main request involves an inventive step. Moreover, the subject-matter of claims 2 to 7, which are appendant to claim 1, similarly involves an inventive step.

5. Consequently, the auxiliary requests of the appellant need not be considered.

## Order

**For these reasons it is decided that:**

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the following documents:

   (a) claims 1 to 7 filed as main request on 29 April 2005;

   (b) description, pages 2 and 3 presented during oral proceedings, and pages 4 and 5 and page 6, column 9, lines 1 to 18, as granted;

   (c) drawings, Figure 1, as granted.

The Registrar: The Chairman:

M. Dainese W. Moser