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Non-CFC metered dose inhalers: the patent landscape

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Abstract

There have been many patent applications to the European Patent Office over the past decade involving the transition of pressurised metered dose inhalers from the CFCs to non-CFC propellants. In addition to those where formulations are changed, there are those relating to specific drugs or drug classes, processes of manufacture and modifications to the container/closure system. Many of these have been opposed, usually on the grounds of obviousness. However, due to the length of time for the opposition process and the fact that there are few non-CFC pressurised inhalers on the market yet, the complete picture of which patents are valid has yet to unfold. © 1999 Elsevier Science B.V. All rights reserved.

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1. Introduction

Any company involved in research and development should take steps to protect the fruits of its labours. The pharmaceutical industry is no exception and invests considerable resources in research and to generating and enforcing intellectual property rights by means of patents and trademarks. A patent gives the owner the right to prevent others from using the invention and is a powerful weapon to gaining an exclusive market position. A patent does not give the owner the right to use his patented invention since it is conceivable that in practising his invention he will be infringing one or more earlier patents. Thus, in addition to acquiring its own intellectual property, it is important for a company to continuously monitor the patenting activities of its competitors and to intervene to attack patents which may be relevant to potential commercial products.

2. The European patenting process

In order to obtain a patent the applicant must file a patent application which discloses the invention in a manner sufficiently clearly and completely for it to be carried out by a person skilled in the art (European Patent Convention, Article 83). The claimed invention must be new and involve an inventive step (European Patent Con-

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vention, Article 52) having regard to the state of the art. The state of the art comprises everything made available to the public in any manner before the date of filing of the application (European Patent Convention, Article 54).

The prosecution of a patent application can take several years before a patent is granted. International Patent Applications (PCT) and European Patent Applications (EP) are published 18 months from the priority date (date of first filing) and thus patent literature provides an interesting window through which one can gain some idea of the research activity of a competitor, long before the products reach the stage of clinical trials or marketing. The prosecution file of a published European patent application is open to public inspection and it is possible to follow the arguments of the Patent Office Examiner and the patent applicant as the merits of the invention are assessed prior to the grant of a patent.

A European patent may be opposed within 9 months of grant. This provides an opponent with the opportunity of destroying a patent covering up to 17 countries in a single action. After the opposition period has expired it is only possible to nullify a European patent by taking action in each separate country. Opposition proceedings are primarily based upon written arguments terminating in Oral Proceedings (a Hearing) before the Opposition Division, which, unlike many proceedings before national courts, rarely lasts for more than 1 day. The decision of the Opposition Division is subject to appeal to the Board of Appeal. The appeal proceedings follow a similar pattern to the opposition procedure and terminate in Oral Proceedings. The decision of the Board of Appeal is final. Opposition proceedings are likely to take 2 years and a further 2 years for appeal proceedings; although a longer time frame is not unusual.

The opposition procedure before the European Patent Office is an extremely useful forum in which to attack a competitor's patent. It is rare that a patent proprietor will take steps to enforce a European patent whilst it is under opposition. Successful opposition will result in the patent being revoked in all of the designated countries, partial success will result in the scope of the patent being narrowed in all designated countries. Unsuccessful opposition will result in the European patent being maintained, but does not preclude the opponent from attacking the European patent before the national courts. It will come as no surprise to learn that in the field of metered dose inhaler (MDI) products involving alternative (non-CFC) propellants, a very high percentage of European patents have been opposed, often by several opponents.

3. A review of European patent applications

A review of published European patent applications reveals the tremendous amount of research effort which has been made in formulating new MDI products by numerous companies and universities. The common theme of most of the applications is the use of hydrofluoroalkanes (HFA), particularly 1,1,1,2-tetrafluoroethane (P134a) and 1,1,1,2,3,3,3-heptafluoropropane (P227) as a propellant in MDI formulations. However, these propellants are clearly not 'drop-in' replacements for the traditional CFCs, they do not dissolve the conventional surfactants which were used in CFC MDI formulations and problems of formulation stability and compatibility with valve components arise. The solutions to these problems disclosed in the patent literature are many and varied. Some patents are restricted to the formulations of particular drugs or drug classes and others teach formulations of applicability to a range of drugs. Further patent publications provide new processes of manufacture or modifications to the container/closure system. The approaches to MDI formulation disclosed in the European patent literature may be loosely classified as follows:

3.1. Applications relating to MDI formulations applicable to a range of drugs in which the propellant system comprises HFA in admixture with other propellants or modifiers

EP 0372777*: P134a + polar adjuvant + surfactant.
EP 0384371*: P227 mixtures with other propellants.

EP 0499344*: P134a + alcohol or hydrocarbons + surfactant.
EP 0550031*: P227 + surfactant.
EP 0513099: P227 mixtures with other propellants.
EP 0514415*: HFA mixtures with other propellants.
EP 0779351: HFA propellant mixtures.
EP 0789557: HFA propellant mixtures.

3.2. Applications relating to MDI formulations applicable to a range of drugs for which (a) the drug is coated with surfactant or (b) specific types of surfactants are employed which are new to MDI formulations

(a):
EP 0493437*: Surfactant coated drug.
EP 0556239: Surfactant coated specific drugs.
EP 0556256*: Surfactant coated + cosolvent.
(b):
EP 0504112: Acetylated monoglycerides.
EP 0513127: Soluble fluorinated surfactants.
EP 0526481: Fluorinated carboxylic acid derivatives.
EP 0536204: Perfluorosulfonamide alcohol phosphate esters.
EP 0536235: Polyoxyethylene surfactants.
EP 0536250: Soluble fluorinated surfactants.
EP 0605578*: Polymeric surfactants.
EP 0630229: Tagat® surfactants.
EP 0633019: Polyoxyethylene glyceryl esters.
EP 0689423: Diol-diacid polymers.
EP 0689424: Ester/amide/mercaptoester derivatizedpolymers.
EP 0731688: Protective colloid.
EP 0777467: Polyglycolized polyglycerides.

3.3. Applications relating to MDI formulations which are free from surfactant

EP 0553298*: Beclomethasone dipropionate solutions.
EP 0587790: HFA 134a optionally with other ingredients.
EP 0588897: HFA 227 optionally with other ingredients.
EP 0616523: With specific drugs.
EP 0616524: Specific drugs other than those for the above.
EP 0616525*: Suspensions with cosolvent.
EP 0617610*: With performance criteria.

3.4. Applications relating to the preparation of MDI formulations of specific drugs or drug classes

EP 0553298*: Beclomethasone dipropionate.
EP 0561166: Flezelastine.
EP 0625046: Beclomethasone dipropionate.
EP 0626173: Fusafungine
EP 0658101: Beclomethasone dipropionate.
EP 0691842: Lidocaine.
EP 0735884: Flunisolide.
EP 0775484: Beclomethasone dipropionate.
EP 0797431: Polypeptide.
EP 0814769: General anaesthetic.
EP 0814793: Prilocaine.
EP 0817611: Butixocort.
EP 0848607: Glyceryl trinitrate.

3.5. Applications relating to MDIs involving the use of (a) special valve seals or (b) lining of the aerosol container

(a):
EP 0562032.
EP 0673857.
EP 0697002.
EP 0708805*.
(b):
EP 0642992*.
EP 0820279.
EP 0820322.
EP 0820333.
EP 0820414.

3.6. Miscellaneous applications relating to MDI formulations involving (a) other excipients and (b) special process steps

(a):
EP 0673240: Acidic drug stabilizers.
EP 0799024: Sugars.
EP 0804157: Tocopherol.

(b):
EP 0643166: Lyophilization.
EP 0655237: Spray-drying.
EP 0851753: Kneading.

3.7. Processes of manufacture, such as variations on the pressure filling process and in-situ milling

EP 419261: In-line purge with propellant.
EP 689515: Propellant purge of MDI can.
EP 768114: In-situ micronization.

4. Discussion and conclusions

The authors do not pretend the above information is exhaustive. Also no distinction is made between granted patents and applications. Those cases marked with an asterisk are known to have been/are subject to opposition proceedings. It is noteworthy that patents in Section 3.1, relating to the use of propellant mixtures, have been subject to multiple opposition. Much of the opposition is fought over the dividing line as to what may be considered to be a matter of routine trial and experiment with a predictable outcome of success(obvious and non-patentable) and what may be considered to involve a creative or unpredictable contribution (inventive and patentable). Judgements in such matters often include an element of subjectivity and the outcome of opposition and appeal proceedings is by no means predictable and it is not unusual for the Appeal Board to amend or reverse a decision from the Opposition Division.

European Patent Nos. 0372777 and 0553298 were upheld by the Opposition Division but revoked by the Board of Appeal. The other oppositions have not progressed to the appeal stage.

There are many opposition battles being fought before the European Patent Office and no doubt there will be many more as applications proceed to grant. Currently there are very few non-CFC MDI formulations on the market and the authors are not aware of any infringement actions in Europe.