Protecting Combination Products

Manuel Campolini looks at the intellectual property issues surrounding fixed-dose combination products in the EU.

The value of fixed-dose combination products, i.e. the combination of two or more active substances within a single pharmaceutical form of administration, seems to be gaining increased recognition. In the past, the emphasis was on objections to issues such as the lack of flexibility surrounding the use of such products coupled with a perceived restrictive approach of some regulators. Later on, increased awareness of the difficulties of treatment compliance in the context of HIV/AIDS – where patients are often required to take a substantial number of different medicines – changed this emphasis. Fixed-dose combination products were progressively viewed as developments that deserved more support.

To cite an example, Regulation (EC) No 816/2006 on the compulsory licensing of products for export to developing countries includes a specific reference to fixed-dose combination products. Moreover, in the context of access to medicines by sub-Saharan populations, where patient compliance is much more of a challenge, some NGOs have bitterly criticised pharmaceutical companies for failing to join forces to develop fixed-dose combinations of their respective products.

This article will examine the legal issues surrounding the protection of combination products, as well as specific features relating to the combined use of separate products, although the use of an active substance together with a medical device will not be examined.

Data and market exclusivity

The European Union (EU) pharmaceutical legislation does not include an explicit provision dealing with the granting of data and market exclusivity to fixed-dose combination products. The previous Notice to Applicants (NtA) indicated that strictly speaking, any combination is a new and unique medicinal product requiring a separate marketing authorisation and [SmPCF]. This statement, which represented the common view of the European Commission and the member states, could be interpreted as implicit recognition of a specific data exclusivity regime for combination products.

However, even if a new fixed-dose combination of two different and known active substances results in a new substance, the restrictive approach adopted by the European Court of Justice (ECJ) on data exclusivity – which started with the 1998 judgment in case C-368/96 (Generics UK) concerning essential similarity – represented a cause of concern for innovators. This concern was later reinforced by two factors. Firstly, the introduction of the concept of the “global marketing authorisation” in the revised pharmaceutical legislation (Directive 2001/83/EC, as amended by Directive 2004/27/EC), whose underlying rationale was to deny data exclusivity for important and costly developments of existing substances. And secondly, the broad definition of generic products included in the revised Article 10 of Directive 2001/83/EC which includes even different isomers, for instance.

The revised NtA retains its previous text but also adds that … a new ‘combination’ medicinal product will have an independent period of data exclusivity and market protection from its first authorisation within the Community and that an authorisation for a ‘combination’ medicinal product is not considered to fall within the scope of the global marketing authorisation for the individual active substances. The precise scope of the protection is as follows: it is the specific set of new data submitted to register the combination itself that is protected by data and market exclusivity (8+2+1). It is still permissible for a competitor to rely on data previously submitted to register the individual active substances whose various types of protection have already expired.

Combined use of two separate active substances

In a number of circumstances, it is impossible or inappropriate to develop a fixed-dose combination of two or more substances, so the products are administered separately, each being subject to a separate authorisation. This situation can be quite complex. One or both substances can be new or known. They may have been originally registered for the same or for different indications. The summary of product characteristics may require, or simply allow, co-administration of the products, or administration of one of them with a posology that can vary according to the products’ use in monotherapy. Their respective forms could be different, e.g. injectable/tablet. Their administration might be simultaneous or successive, e.g. giving the first product only during a certain period of time followed later by the second product.
As a result of the new “global marketing authorisation” concept, the data and studies specifically generated to substantiate the safety and efficacy of such a combined use may not benefit from data/market exclusivity in a number of situations, and the relevance of such an approach is questionable. Substantiating the safety and/or efficacy of combined use of two separate products may also involve extensive and costly clinical research, even though there are examples where the new combined use dramatically increases the efficacy of the treatment. Where data/market protection is available, it might be valuable if the presentation of the product(s) is new, eg a new pharmaceutical form or a new delivery system and posology.

Combination packs, understood as the inclusion in the same packaging of two separate products with different active ingredients but under the same trade name, might in some cases address off-label use and consequently justify this type of R&D. During the 49th meeting of the Pharmaceutical Committee in March 2000, the European Commission stated that under the current legal framework, and contrary to fixed-combination products, combi-packs or convenience packs cannot be the subject of one marketing authorisation. The committee took note of this position. Member states apparently consider combination packs acceptable if there are strong arguments for the provision of a combination package with respect to benefit to public health or where the use of a combination package is more user friendly for the patient or healthcare professional … commercial reasons are not considered a valid justification for the provision of a combination package.\(^6\)

The balance of interests could only be assured by a complex case-by-case assessment.

**Patents**

Fixed-dose combination products can benefit from the 20-year period of patent protection provided that the patentability criteria are met, ie novelty, inventive step and industrial application. Patent protection may be available for the combination of two or more new or known active substances. The optimum patent strategy for combination products could be difficult to implement – it should take into account the advantages and risks involved in either claiming the combination when the patent is filed with respect to the more recent active substance, or claiming it later, which could extend the protection period but might also be rejected because of a lack of novelty/inventive step.

The patentability of the combined use of two separate active substances/products is more challenging as there may be significant technical hurdles to overcome. One such hurdle is the European exclusion from patentability of methods of treatment, for example when a specific posology is proposed. Other obstacles lie in the novelty and inventive step requirements. Patentability may be envisaged notably when the combined use improves the safety of one of the products and/or results in improved efficacy that was not foreseeable. Of course, when such an improvement results from off-label experiments conducted independently by hospitals, novelty may be destroyed. The combined use of separate products in a new indication, or when one of the products is patented or labelled for a different indication, may play a role in determining whether patent protection is available or not.

The fact that the separate products already benefit from product patent protection and/or are marketed by different companies does not prevent the patentability of the combined use, at least in principle. In this latter case, patent infringement relating to the marketing of the products might be an issue.

**Supplementary Protection Certificates (SPCs)**

The SPC is a specific intellectual property title that allows a de facto extension of the protection of a pharmaceutical product deriving from a “basic patent”. It was introduced in the EU by Regulation (EC) No 1768/92 and aims to compensate for the time lost between the initial patent filing and the marketing approval of the patented substance as a medicinal product\(^7\). The extension is limited by two cumulative ceilings: a maximum of five years following the expiry of the basic patent and a maximum of 15 years from the first approval of the product in the European Economic Area (EEA).

**Fixed-dose combination products**

One of the advantages of an SPC for a combination product lies in the fact that it may end long after the SPC for one of the active ingredients, notably in respect of the 15-year ceiling. This matter is relatively complex and requires particular attention. In the UK for instance, Takeda had a patent for lansoprazole and later on obtained a marketing approval for a fixed-dose combination of lansoprazole with antibiotics. The initial patent for lansoprazole did not claim the combination and this latter was probably not patentable subsequently. The granting of an SPC for the combination product was refused because the basic patent related to one active ingredient only\(^8\). The English court did not refer the matter to the ECJ as it was considered “acte clair”. A Swedish court took a similar approach in another case.
New substance allowing controlled release of a known active ingredient

In 2006 the ECJ limited the possibility of granting an SPC for combination products in a case involving the US Massachusetts Institute of Technology (MIT). MIT is the holder of a patent covering a substance called polifeprosan, which was developed to provide a biodegradable matrix for use in biomedical applications. Carmustine is an off-patent active ingredient previously approved in the EU as a cancer treatment. Gliadel is a new formulation of carmustine combined with polifeprosan and is indicated for the treatment of recurrent brain cancers. Polifeprosan has no therapeutic effect on its own but allows the controlled release of carmustine. This combination substantially improves the therapeutic effect of carmustine, and consequently the life expectancy of patients.

An SPC may be granted to a product protected by a basic patent that has been subject to a first marketing authorisation as a medicinal product. Regulation (EC) No 1768/92 defines a product as an active ingredient or combination of active ingredients, and a medicinal product as any substance or combination of substances produced for the treatment or prevention of disease in human beings or animals. No SPC can be granted to carmustine – but could it be obtained for Gliadel, ie for the combination of carmustine and polifeprosan? Unlike the UK and the French patent offices, the German patent office refused to grant an SPC because polifeprosan is not an active substance having its own therapeutic effects. MIT argued that polifeprosan was neither an excipient nor a mere auxiliary component, but an essential component of Gliadel. The matter was referred to the ECJ.

In his opinion on 24 November 2005, the advocate general concluded that Gliadel should benefit from an SPC as “the combination at stake represents a major innovation, resulting from long, costly research, which the regulation is precisely seeking to protect”\(^{10}\). He said that a large proportion of medicinal products benefit from a new marketing authorisation even in cases of minor change and that an SPC “cannot be granted every time the characteristics of a medicinal combination are slightly modified”. He suggested patent offices assess the marketing authorisation in order to determine the existence of therapeutic innovation. More importantly, he stressed that “it is … the necessity of the excipient to the therapeutic efficacy of the active ingredient that must be the determining factor in ascertaining whether a combination of these two substances is covered by ‘combination of active ingredients of a medicinal product’”.

However, the ECJ considered that no SPC could be granted as “the expression active ingredient is generally accepted in pharmacology not to include substances forming part of a medicinal product which do not have an effect on their own on the human or animal body”. The court ruled that the concept of combination of active ingredients does not include a combination of two substances, only one of which has therapeutic effects on its own for a specific indication, the other rendering possible a pharmaceutical form which is necessary for the therapeutic efficacy of the first substance for that indication. Another case is still pending before the ECJ\(^{11}\).

The ECJ also referred to the commission’s explanatory memorandum for its initial SPC proposal, which stated that “only one [SPC] may be granted for any one product, a product being understood to mean an active substance in the strict sense. Minor changes to the medicinal product such as a new dose, the use of a different salt or ester or a different pharmaceutical form will not lead to the issue of a new SPC”\(^{12}\). This is not the first time that the ECJ has tackled the issue of salts\(^{13}\). However, by contrast the NtA contains a definition of a new active substance that has not been modified since the adoption of the new legislation and which says that a new salt or ester with the same moity results in a new active substance if the change leads to differences in properties with regard to safety and efficacy\(^{14}\). Article 10(b) of Directive 2001/83/EC refers to “significant” differences. Should the use of a different salt result in a new active substance, exclusion from the benefit of an SPC would be illogical.

Pricing and reimbursement

Pricing and reimbursement systems are highly heterogeneous, as every country has its own system, but in general, when a combination product provides a marked therapeutic benefit, the company is more likely to receive a better price and reimbursement level. This could be the case when, following extensive research and labelling, the use of two separate products results in such an improvement. In this case off-label use may erode the product revenues, for example when the standard protection for one of the products has expired.

A fixed-dose combination of existing substances, defined as a new and unique medicinal product, may also delay the automatic price erosion related to patent expiry on individual substances. In Belgium, the decision to reimburse a generic product leads to an automatic 30% reduction in the reimbursement basis of the reference product and is likely to generate a
corresponding price reduction. Even in the absence of a patent, a fixed-dose new combination product might avoid this price reduction as the existence of data exclusivity would prevent generic entry for ten years unless it was easy for a generic company to repeat the data used to approve the combination.

Belgium also introduced a reference pricing system in 2005 under the heading “group revision”, although this is only applicable to off-patent reference products and generics. Of course, the situation is much more complex and the authorities have a wide range of tools in such controversial matters, but the economic value of combinations of existing molecules should not be overlooked.

**Conclusion**

It is logical to presume that there are a number of valuable developments – notably those resulting from incremental innovation – that are not being conducted because the risk that they would be immediately available to competitors is too high. This situation reflects to some extent a restrictive approach by the EU authorities where medicinal products are concerned. It also leads companies to focus on developments that benefit from effective patent protection. Finding a solution to this complex problem – ie, providing greater health benefits by effectively protecting the research surrounding such developments – will not be easy, and will have to take a large number of variables into account.

**References**

2. Notice to Applicants, Chapter 1 (February 2004), page 15

**Incremental innovation may be lost because companies calculate that the risk of competition is too high**

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