Patenting Combination Products

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Pharma companies are increasingly looking to combination products as a source of much-needed revenue – but the patent situation for such products is far from straightforward.

The value of combination products to the pharmaceutical industry is increasing all the time. As the risk and cost of bringing new chemical entities to market increases, pharmaceutical companies are looking to combination products to prolong exclusivity for their compounds and fill gaps in their pipelines.

Supporting Technical Data for Combinations – Is it Plausible?

Patent law requires that inventions must be novel and exhibit an inventive step in order to be patented. Under the European Patent Convention, an invention is considered novel if it has not been made available to the public in any way before the patent application was filed. If one of the active substances in a combination is itself novel, combination products can be patented as part of the basic patent claiming this active substance. Most patent applications for new pharmaceutical active ingredients generally include text in the description which mentions potential combinations with other known actives in the same and in other classes. This provides a basis for claiming combinations at a later stage if these become of commercial importance during development of the new active, and is particularly important in view of the Supplementary Protection Certificate (SPC) decisions discussed below.

Keywords

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If both of the actives are known, but the combination is not, it is possible to file a separate patent application specifically claiming the combination. To exhibit an inventive step, the combination must not be obvious to a person skilled in the art. The European Patent Office (EPO) generally assesses inventive step by considering whether the invention exhibits a technical effect not exhibited by the closest prior art. Technical data are usually required as evidence of such a technical effect. For combination products, data demonstrating that the combination exhibits a synergistic effect (greater than the additive effect of the two actives taken alone) will frequently be persuasive, as will data that demonstrate that the combination is responsible for another unexpected technical effect, such as the presence of the second active improving the pharmacokinetics or metabolism of the first.

Recent case law from the EPO's Boards of Appeal has focused on whether the data required to support inventive step needs to be included in the patent application as filed, or whether it can be filed at a later stage if requested by the EPO. In decision T1329/04, the Boards of Appeal doubted that it was plausible from the application as filed that the claimed invention exhibited the required technical effect, and refused to consider supporting data filed during prosecution. The invention claimed in the patent was consequently found to lack inventive step.

Thankfully, two more recent decisions (T578/06 and T1642/07) have disagreed with this earlier decision, and shifted the initial burden of proof back to the EPO to substantiate doubts about the plausibility of the alleged technical effect. In these decisions, the Boards ruled there is no requirement for the patent application as filed to have experimental evidence of the claimed technical effects, unless doubts regarding the necessary technical effect are substantiated.

These decisions are of particular importance to combination pharmaceutical products. If at all possible, it is always best to include some data

that support the technical effect exhibited by the combination in the application as filed, particularly if there could be any doubt that the combination exhibited this effect. Even where this is not the case, it may still be possible to argue that the two later decisions should be followed, and that experimental data filed during prosecution to confirm the alleged technical effect should be taken into account by the EPO. Further data can be filed during prosecution in order to support that in the application as filed – for example, to demonstrate that synergy is exhibited for combinations across a class of pharmaceutical active ingredients and is not confined to a combination of two specific actives. However, such data may only be admissible if there is no substantiated reason to doubt the plausibility of the alleged technical effect.

SPCs for Combinations – Is it Specified?

Supplementary Protection Certificates (SPCs) for pharmaceuticals were introduced across the EU in the early 1990s. The aim of SPCs is to compensate the patent holder for the patent term lost due to the need to obtain regulatory approval. In the EU, SPCs can extend the term of protection for such a patented product by up to five years (with a further six months possible if paediatric studies are completed). As the term of the SPC is often the time when the product achieves its peak sales, obtaining SPCs is of critical importance to the pharmaceutical industry.

The award of SPCs for products containing a combination of active ingredients has been a controversial matter in EU countries. This issue is particularly important for vaccines, which frequently contain a combination of active ingredients; health authorities often insist that multiple vaccines be administered in a single dose to minimise the cost and inconvenience to patients. Over recent years, a number of conflicting decisions have issued from national courts regarding SPCs for combination products, and a number of questions were referred to the Court of Justice of the EU in order to clarify the law (the Medeva and related cases). Essentially, the CJEU had to decide between two opposing arguments: the 'infringement test' (in other words, if the claims of the basic patent recite active ingredient A, an SPC can be granted for any approved pharmaceutical product containing A either on its own or together with any other active), and the 'specified test' (in other words, if the claims of the basic patent recite A, an SPC can only be granted for A and not a combination of A with another active). The CJEU preferred the 'specified test', ruling as follows:

- An SPC must not be granted for an authorised medicinal product which is a combination of two active ingredients (A + B) if the literal wording of the basic patent claims A in isolation. This applies even if the claims use 'comprising' or similar language which does not exclude the presence of another active
- An SPC must not be granted for an authorised medicinal product which is a combination of A + B if the literal wording of the basic patent claims a combination of A with another unspecified active ingredient
- An SPC may be granted for an authorised medicinal product which is a combination of A + B if the literal wording of the basic patent claims A in combination with the specified active ingredient B
- An SPC may be granted for an active ingredient (A) if the wording of the claims of the basic patent relied on specifies A, even if the authorised medicinal product contains not only that active ingredient but also other active ingredients (A + B, A + C and so on)

It is unclear from the rulings how specific the claim language has to be for the product to be 'specified' in the claim wording. For example, is product B sufficiently 'specified' if it is defined by therapeutic class (for example, a combination of A and an antibiotic) or by a general formula that covers the individual active ingredient but not does specifically recite it? In addition, do biologic patents that claim, for example, antibodies to a particular antigen without disclosing the antibody 'specify' the antibody that is eventually authorised? With these questions in mind, the UK Patents Court has recently referred another SPC combination case to the CJEU to clarify the matter further.

On a more positive note for applicants, in a more recent decision (*Novartis v Actavis*), the CJEU ruled that if an SPC is granted for a single active A, the SPC owner could enforce it against a competitor marketing a combination of actives A + B. However, the decisions reached in the *Medeva* and related cases, as well as denying SPC protection for the products in question, may also leave the validity of already granted SPCs for some combination products in some doubt.

Drafting and Amending Combination Cases – Our Recommendations

In view of these decisions, the following changes are recommended for future pharmaceutical patent applications covering a single active ingredient A, either as a species or as part of a broader genus of compounds:

New Applications: If a likely commercial product A has already been identified, new applications should include claims explicitly directed to any specific combination products (A + B, A + C, and so on) considered likely to be of commercial interest at the time the application is filed. The specific actives B, C and so on, may be marketed products (or those currently undergoing clinical trials) for the same therapeutic indication or related indications as A. Before deciding to include such combinations explicitly in the text, the possible prior art effect on a later patent application specifically directed to such combinations should be considered.

Pending European Patent Applications: If active ingredient A has received or is likely to be submitted for regulatory approval, these applications should be reviewed to ensure that any specific combinations of actual or potential commercial importance, but which are currently disclosed in the description only, are included in the literal wording of the claims when granted.

Granted European Patents: If active ingredient A has already received, or is likely to be submitted for regulatory approval, these should be reviewed to consider whether any specific combinations of actual or potential commercial importance which are disclosed in the application as filed, but not specified in the literal wording of the claims as granted, could be claimed using the EPO's post-grant limitation procedure. Such a limitation may not extend the protection conferred by the patent. However, if the granted patent contains a claim to a combination of A with another unspecified active ingredient, such a claim could be validly limited by specifying the active as B, C, and so on.

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