PATENT APPLICATIONS IN THE PHARMACEUTICAL FIELD

Introduction

Individuals and companies file patent applications for a variety of reasons. Decisions as to which technological developments merit patent protection, the territories in which patent protection is sought, and the point in time at which a patent application is filed can be driven by many factors, including cost, legal considerations, the extent of supporting experimental data available, and above all the commercial objectives for the technology. This Briefing aims to provide an overview of some of the issues that may inform such decision steps in the pharmaceutical field. We also look at some specific legal considerations that can arise in the emerging markets of India and China.

Patent Applications - Importance in the Pharma Field

In some industries it is common to protect technological developments as confidential information, but this happens less often in the pharmaceutical field. A possible exception concerns inventions relating to research/screening methods where the valuable output is information. Generally, though, the regulatory framework means that patent protection is indispensable in recouping the costs associated with commercialising a new drug.

Thus, patent protection can be used to protect markets for the owner and/or licensees, both in the short term by denying competitors access to products/processes, and also in the longer term by deflecting competitive research and development. An effective patent portfolio is thus generally key in enabling the owner to develop its own manufacturing capacity, create revenue by licensing to one or more manufacturers, or just “sell on” the technology once enough work has been done to show that the product has commercial potential.
Territorial Coverage: Where to File and Why?

A successful pharmaceutical product with robust patent protection can generally provide a profitable revenue stream in most countries in which it is launched. Consequently, large pharmaceutical companies routinely pursue patent protection in a far wider array of countries than are seen in most other technical fields.

Smaller pharmaceutical companies with less financial resource that are looking to sell or license the technology before completing all of the necessary clinical trials may often elect more limited territorial coverage for cost reasons. While this may reduce the overall value of the patent estate, the inclusion of even a limited number of key markets may well still be enough to attract a commercial partner if the technology at issue is compelling.

When it comes to choices about territorial coverage, setting aside technical considerations such as possible variation in the prevalence of the target disease and responsiveness to the envisaged treatment in a given patient population, as a general rule the three first territories on a filing list will be the USA, Europe and Japan, as these are the three largest markets. Expanding beyond that will typically take in all the so called “BRIC” countries (Brazil, Russia, India, and China) along with the smaller but well developed markets of Australia, Canada and South Korea. Mexico is often added too, partly due to its proximity to the USA. Other States that are often added because patent protection is available there relatively cheaply, include Israel, New Zealand, Singapore, Malaysia and South Africa.

A convenient approach for handling territorial coverage across a portfolio of multiple patent applications can be to group all countries of potential interest together in different tiers depending on their importance. Thus, tier 1 could include just the USA, Europe and Japan, with subsequent tiers incorporating progressively more territories. A given case can then be assigned to a tier depending on its importance.

For completeness it is also worth noting here that legal considerations can also influence decisions on which States to cover, as certain types of invention may not meet patentability requirements in some countries. Thus, difficulties may arise with medical use claims in India, selection inventions in Brazil, computer related inventions in the USA and Europe, and biotechnology inventions in the USA, while the scope of claim likely to be available can be restricted in countries such as China, South Korea and Japan depending on the extent of exemplification in the application.

What Supporting Data is needed in a Pharmaceutical Patent Application?

This is a consideration that can play an important role in governing the point in time at which to file a patent application. As a general rule, \textit{in vitro} data in an appropriate test protocol is enough to support a patent application for a new drug, or for a new medical use of a known drug. At the European Patent Office, for example, Technical Board of Appeal Decision T1045/98 explained that:
“It is an accepted principle of the case law that, for the purpose of patent protection of a medical application of a substance, a pharmacological effect or any other effect such as an effect observed either in vitro or on animal models is considered to provide sufficient evidence of a therapeutic application if for the skilled person this observed effect directly and unambiguously reflects such a therapeutic application.”

This is not, though, a hard and fast rule. If the prior art teaches or suggests that the compounds at issue will have *in vitro* activity, and the invention is therefore presented as a finding that the drugs at issue have clinical efficacy despite some reason in the art to think that that might not be the case, it is likely that clinical data will be needed to support the claimed invention.

**When is Comparative Data Necessary?**

There is a helpful line of caselaw at the European Patent Office which suggests that objections of lack of inventive step should not routinely be raised merely because structurally similar compounds with similar activity are disclosed in the prior art. One leading case is T852/91, where the Board explained that

“To deny inventive step for novel chemical compounds because of their "structural similarity" to known chemical compounds amounts to an allegation that a skilled person would have reasonably expected the same or similar usefulness of both the known and the novel compounds as the means for solving the technical problem underlying the application in question. Such an expectation would be justified, if the skilled person knew, be it from common general knowledge or from some specific disclosure, that the existing structural differences of the chemical compounds concerned were so small that they would have no essential bearing on those properties.” Reason 8.2, emphasis added.

If, though, a Patent Office Examiner is convinced that the prior art teaches that biological activity will indeed be achieved with the compounds at issue, it is likely (at the EPO, at least), that comparative data will be needed to demonstrate an inventive step. Comparative data is often required, for example, in the following situations:

- compounds are claimed which are structurally distinct from the compounds exemplified in a prior art patent application, but which are embraced by a Markush formula in the prior art patent application;

- the invention claimed is a combination of known drugs;

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1 See also T643/96, T2402/10 and section I-D-9.8.2 of the textbook “Case Law of the Boards of Appeal of the European Patent Office”.

the invention is a new salt form, polymorph or stereoisomer of a known compound.

Comparative data can be filed to demonstrate some unexpected technical advantage associated with the claimed invention, as compared with the prior art. Any technical effect which is "derivable from the application as filed" can be used to support an inventive step in this way. The EPO does not require there to be explicit mention of the technical advantage in the specification as filed - any technical advantage which would be understood "as implied by or related to the technical problem initially suggested" can be used in support of an invention.²

Thus, for example, if the invention described in the original specification is a bronchodilator drug suitable for inhalation, comparative data evidencing a reduction in toxicity or an improvement in stability when drug particles are micronized would be likely to be admissible as sufficiently related to the original technical problem. A finding that the drug at issue promotes hair growth in balding patients would not!

Does Supporting Data need to be in the Application as Filed?

Situation at the European Patent Office (EPO)

The leading case at the EPO on this particular issue is T1329/04 (Johns Hopkins). The claim at issue in that case concerned a DNA sequence encoding a protein "having GDF-9 activity". There was nothing inventive in making the DNA sequence - the inventive step, if any, was said to lie in a disclosure that the DNA coded for a therapeutically useful protein. However, the specification contained no supporting data - it just explained that expression of GDF-9 is localized in ovarian tissues, and asserted that the protein was therapeutically useful.

The Board of Appeal identified two separate hurdles that needed to be overcome for a finding of inventive step:

(1) firstly, there must be enough evidence in application as filed to make it at least plausible that a solution was found to the problem purportedly solved; and

(2) secondly, if hurdle (1) is overcome, it is permissible to then rely on further data adduced after filing in connection with inventive step.

The Board in case T1329/04 considered that the specification attributed various effects to GDF-9 "tentatively and presumptively", and that while post-filed evidence did show that the claimed DNA sequence coded for a therapeutically useful protein, this was "the first disclosures going beyond speculation". The post-filed data was accordingly ignored.

² See Guidelines for Examination at the European Patent Office at G-VII-5.2, from which the quotations are taken.
The approach taken in Decision T1329/04 is not reliably followed at the EPO, though, particularly in the chemical field. When compounds or compositions are claimed per se, it is often possible to file a patent application with little or no supporting data and provide the necessary support after filing. When the claims at issue are medical use claims, though, the EPO does generally take a more consistent approach, and requires at least some supporting data in the specification as filed.\(^3\)

**Situation in other States**

In our experience, countries in which the Patent Offices are often willing to take post-filed data into account include the USA, Russia, Australia and New Zealand, provided that the technical effect being evidenced was predicted in the original specification. On the other hand, in Japan, Canada and South Korea, the Patent Offices are generally unwilling to take into account post-filed data. The same is also usually true in China, although practice is slowly becoming a little more liberal there.

**Specific Issues to Bear in Mind when Pursuing Patent Protection in India**

India has historically been perceived as relatively hostile to patents, particularly in the pharmaceutical field. However, it is now a signatory to the TRIPs agreement and corresponding patent law amendments came into force on 1 January 2005, with the consequence that patent protection for pharmaceutical products per se became available. However, there are legal provisions in India which are designed with the aim of making it difficult to cover all technology advances in the pharmaceutical field. Some of these provisions are discussed below.

**Section 3(d)**

Section 3(d) precludes from patentability:

> “the mere discovery of a new form of a known substance which does not result in enhancement of the known efficacy of that substance or the mere discovery of any new property or new use for a known substance or the mere use of a known process, machine or apparatus unless such known process results in a new product or employs at least one new reactant”

Section 3(d) also explains that:

> “salts, esters, ethers, polymorphs, metabolites, pure forms, particle size, isomers, mixtures of isomers, complexes, combinations and other derivatives of known substances shall be considered to be the same substance, unless they differ significantly in properties with regard to efficacy” (emphasis added)

\(^3\) See T609/02 and the discussion at Section II-C-6.2 of the textbook “Case Law of the Boards of Appeal of the European Patent Office”. 
The reference to “efficacy” in section 3(d) was interpreted by the Supreme Court in India as meaning “therapeutic efficacy” after Novartis appealed the refusal of their patent application relating to a beta crystalline polymorph of Glivec (imatinib mesylate). This polymorph had been shown to have improved bioavailability, thermodynamic stability and flow properties, and lower hygroscopicity. However, these showings were not considered to provide the improvement in therapeutic efficacy said to be required by section 3(d).

An objection under section 3(d) may be less likely to arise if the application contains data demonstrating a context in which the relevant characterizing feature can result in an enhanced therapeutic effect. For instance, a formulation with improved stability could be supported by data showing an improved therapeutic effect compared to prior art formulations after being stored under accelerated degradation conditions.

A further approach that may help is to include process claims where possible, directed to methods of manufacturing the pharmaceutical product. That is because the requirement for enhanced activity does not apply to process claims, and a process claim in an Indian patent will cover the direct product of the specified process.

**Section 3(e)**

Section 3(e) precludes from patentability:

> “a substance obtained by a mere admixture resulting only in the aggregation of the properties of the components thereof or a process for producing such substance.”

This section can of course form the basis for objections to claims for combinations of known agents or components. Objections are often raised under Section 3(e) even to a new pharmaceutical product in combination with a carrier or diluent. In our experience, though, objections are less likely to arise if the relative amounts of the various ingredients are specified in the claim. Thus, when drafting patent applications likely to be pursued in India, it is important to include basis for specifying the relative amounts of any components in a composition claim. The existence of a synergistic interaction will generally overcome objections based on Section 3(e).

**Compulsory Licensing in India**

At any time after the expiration of three years from the date of the grant of a patent, any person interested may make an application to the Comptroller for grant of a compulsory licence under an Indian patent on any of the following grounds: (a) that the reasonable requirements of the public with respect to the patented invention have not been satisfied, (b) that the patented invention is not available to the public at a reasonably affordable price, or (c) that the patented invention is not worked in the territory of India.
Western companies have voiced concern about these provisions, particularly following the ruling in the Bayer vs Natco case\(^4\) in which a compulsory license was granted for the drug Nexavar. We set out below specific actions that Applicants/Proprietors can take to minimise the risk of compulsory licenses being granted:

- Avoid significant delays between launching a drug in developed markets and beginning supply in India
  - If delay is inevitable, record and evidence all delays caused by specific objections from the Indian drug authorities, including efforts made to resolve the issues
- Supply drug as widely as possible from the outset
  - If specific medical issues (e.g. training of physicians) prevent immediate supply of the drug to all areas, record evidence of such issues and the efforts made to resolve them
- If possible, arrange for at least a proportion of the drug to be manufactured in India (e.g. set up your own local manufacturing plant or use a licensee)
- Consider pricing very carefully - prepare materials at the outset that could be used to justify price by reference to developmental costs, and/or consider differential pricing
- Be scrupulous in complying with the annual requirement to file a Form 27 (working/non-working statement)

**Specific Issues to Bear in Mind when Pursuing Patent Protection in China**

**Claims Formats**

Swiss style claims are available in China. However, explicit basis must be included in the original PCT application for the relevant claim language, i.e. “Use of \(X\) in the manufacture of a medicament for the treatment of \(\text{diseases}\)”.\(^4\)

**Presentation of Data**

It is important to present the data in the original application in an appropriate manner when drafting an application that will be pursued in China. In particular, general comments such as “selected compounds of the invention were tested and

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“found to have an IC50 of less than 10 nM” will attract objections of lack of sufficiency which cannot be addressed by later providing more detail about the compounds tested.

Thus, it is essential to identify the compounds tested and the results they achieved in the original application. It is not, however, necessary to provide specific test scores for each compound. One approach could therefore be to specify the IC50 score for each compound by specifying that it falls within one of the following three ranges, namely (a) <5 nM, (b) 5-10 nM, or (c) >10 nM.

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14 South Square
Gray's Inn
London WC1R 5JJ
UK

+ 44 20 3077 8600
www.jakemp.com