A patent strategy for genomic and research tool patents: are there any differences between the USA, Europe and Japan?

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The patenting of genomics and research tools, and its effects on the development of therapeutics are attracting considerable attention. Regardless of whether one is in favor of patents for this technology, it is not specifically excluded from patenting in most countries. Accordingly, it is imperative that a suitable global patent strategy be developed and followed to maximize both intellectual property rights and returns on R&D investment.

The patenting of genomics and research tools has generated a lot of attention in the past few years. Regardless of whether one agrees that this technology should be patented and exploited, there does not appear to be any real movement towards restricting the grant of patents in this field. However, there has been a proposal in the USA that would, in essence, open up the licensing of research tools developed with the use of federal funds[1].

As with any technology being protected by patents, a patent strategy is important to maximize both the protection of intellectual property rights and the return on investment in R&D. Patent strategies for genomics and research tools probably do not differ significantly from patent strategies in other highly competitive areas of technology. In this article, we consider several factors that affect the development of such a strategy and also consider whether there are any effective differences between the USA, Europe and Japan.

Patent strategy

It has been said that a patent strategy should be a faithful servant of the corporate business[2]. A company's adopted patent strategy must reflect its business objectives and generally also reflects its stage of development. For example, in its early stages, a company might be interested in establishing exclusivity and market penetration, setting price points, building brand awareness, generating revenue, raising capital, and forging long-term alliances. The same company in a later stage, however, might be more interested in extending its exclusivity, increasing returns, maintaining its market share and accessing additional technology. In addition, a company might be developing its genomics and research tools either as end products or as deliverables for use in its own drug discovery platform, or possibly as a combination of both.

These objectives can best be achieved by a mixture of what can be termed offensive and defensive patents. An offensive patent is often associated with establishing a dominant market position, blocking competitors, generating royalties and raising capital. A defensive patent, by contrast, is associated with blocking competition and serving as a licensing and cross-licensing tool. In today's economy, a global patent strategy is a consideration if a company is to maximize the value of its intellectual property. Most companies will seek patent protection in the countries in which they have primary interests and will often make compromises when it comes to diversifying

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elsewhere. Countries of primary interest will be those in which a market and/or a manufacturing capability exists.

Basics of patent law

Any strategy for patenting genomics and research tools must keep basic patent law fundamentals and requirements in perspective. These include: who has a right to a patent; novelty; inventive step (obviousness); industrial utility (substantial utility); sufficiency of disclosure and clear and concise claims. In the USA, the first person who thinks of the invention (i.e. first to invent) is entitled to a patent, whereas in the rest of the world, the first person to file an application (i.e. first to file) is the one entitled. The invention must not be identical to the prior art (i.e. must have novelty) and must not be a logical step from the prior art (i.e. must have an inventive step or be non-obvious). The prior art comprises all knowledge in the world at the time of the invention or the filing of the patent application, including patents, publications, knowledge and use.

An invention that can only be used for further research lacks industrial or substantial utility. The proposed *Revised Interim Utility Examination Guidelines* recently published by the US Patent Office used the word 'substantial' with respect to utility but the only example of insubstantial utility provided is the use of a complex invention such as landfill[3]. Sufficiency of disclosure requires that the patent application fully describes the invention commensurate to the claim language and describes to a skilled artisan how to make and use the invention. The claims of a patent, and not the remainder of the description, describe the boundaries of the property right.

Although the patentability requirements are basically the same in the USA, Europe and Japan, there can be differences in the application of these requirements in practice. One difference is in the area of inventive step (obviousness) and can be illustrated by expressed sequence tags (ESTs), which are isolated and useful merely as probes for a full-length gene. Such an EST would be considered to lack an inventive step in the European Patent Office because the selection of an EST from a cDNA library for use as a probe would be considered an arbitrary choice of one EST from a group and would not be motivated by a technical problem[4]. The Japanese Patent Office would reach the same conclusion by applying its 'obvious-to-try' standard for inventions directed to nucleic acids[5].

However, such an EST would satisfy the non-obviousness requirement before the US Patent Office because there would be no suggestion in the art for the specific sequence of the EST. Even though the EST in this example might satisfy the US Patent Office about its non-obviousness, it might still not be patentable because a substantial utility might not exist. Another practical difference concerns the number of sequences in a single application. Generally, there will be ten sequences in a US application but only a single sequence in European and Japanese applications.

One major difference in the patent laws of the USA, Europe and Japan is the USA's 'first to invent' system compared with the European and Japanese 'first to file' systems. However, the 'first to invent' system used in the USA might be less of an issue in light of the current US law, which allows inventors in World Trade Organization member countries to prove a date of invention before their priority filing. Despite this difference, it is important to be the first to file in the USA. First, if global patents are sought, being the first to file will be an important consideration in obtaining maximum patent protection in all countries. Second, in the event that there is a contest over being the first to invent in the USA, the first to file has significant procedural advantages. Even in the USA, being the first to file is an important component of any patent strategy. Any differences, as well as similarities, in the patent laws of the individual countries need to be considered when seeking patents and preparing applications for filing in different countries[6–13].

With the above factors in mind, one strategy often proposed for obtaining patents for genomics and research tools contains the following components:

- file applications early;
- file applications on further developments frequently;
- file complete specifications within one year of first filings, and file on any improvements before publication;
- maximize protection for discoveries by obtaining protection for 'downstream' products;
- aggressively pursue any commercially significant embodiments while maintaining any remaining embodiments on hold; and
- periodically review a patent portfolio.

Although these components are inter-related in the patent strategy, we will briefly look at them individually.

File early

Patent rights in almost every country of the world except the USA are based on being the first to file. It is thus imperative that patent applications be filed as early as possible in order to secure appropriate protection for the inventive subject matter. If an application is filed too late, the result could be a complete loss of protection. However, if the application is filed too early, it might be used as prior art against a later completion of the invention.

Within these general parameters, there are several factors that should be considered in determining the proper

time to file the first application. Factors that would dictate an earlier application filing include the intensity of the competition, publication demands by the inventors, desire for publication by the company for valuation purposes, accumulation of relevant prior art (i.e. the progression of knowledge in the art), earlier issuance of a patent as protection against competitors and the value of an earlier priority date as a means to defeat similar patents by others. Factors that would dictate a later filing include the need to provide a complete inventive disclosure, a desire to delay publication of the application in order to maintain a head start and a desire to extend the term of the patent for as long as possible[14].

There is little doubt that competition in genomics and research tools continues to be intense. This alone would dictate that an application be filed as early as possible. The earliest filing date possible is an extremely valuable resource in limiting similar patents by others. There is always a strong probability that an initial application will be filed before an invention is completely finished; that is, the application might not contain a complete disclosure of the invention. The competition for the identification of genes associated with disease, including cancer, is so intense that applications are often filed when a fragment of a gene has been identified and that fragment has been confirmed to be associated with some disease by the identification of mutations in families with the disease. In that instance, the application will probably contain a description of obtaining the full-length gene using the disclosed fragment[15,16]. The desire of both companies and inventors publicly to announce or publish their discoveries also is a driving force behind early filings of partial gene sequences in the genomics field. Filing an application directed to only a partial sequence is important because claims to the partial sequence might be held to dominate the full-length gene. Such claims are part of the patent strategy until such time as the courts in each country determine the scope of these claims.

Although filing an application early is a key component of this strategy, the early-filed application must adequately describe the invention (at least to the extent disclosed in the application) and show that it has definite utility, so that claims supported by the application will have the benefit of the early filing date. A nucleic acid with no known or specified utility will probably not have sufficient utility for the application to maintain the benefit of an early filing date. A lack of sufficient utility for the multitude of ESTs disclosed in the first-generation EST applications has or will prevent the patenting of these ESTs. Second-generation EST applications, which describe utilities for the disclosed sequences, should be sufficient for patenting such ESTs (Ref. 17). Thus, some definite utility must be determined before filing.

File frequently

In light of the first component of the strategy (to file early), it will often be necessary to file several applications to ensure that the complete invention is fully disclosed and that all aspects of the invention are fully covered. As soon as an additional development of the invention is known, an application on that development should be filed so that a filing date is obtained for each new development. These filing dates for further developments should also be as early as possible. For example, when a first application is directed to an EST or a gene fragment, it is important that an application for the full-length gene and its protein be filed as soon as possible thereafter. By filing early for each development, the inventors should be able to minimize the effect of any intervening prior art (prior art that comes into existence between the filing dates of the two applications).

This approach is designed to ensure that the initial inventors will be able to maximize the protection they receive compared with that accorded competitors for inventions flowing from the original discovery. For example, consider a gene associated with a disease. An application is filed that is directed to the gene and to those uses that would naturally flow from the knowledge of the gene. As the biological properties and function of the gene are determined, a further application is filed directed to that additional subject matter and to those uses that would naturally flow from the new knowledge, which in turn provides further support for the original disclosure. In order to carry out this part of the patent strategy effectively, it is crucial that close communication be maintained between the scientists and the patent attorney so that patent application drafting and prosecution tracks the scientific progress of the discoveries.

One issue to be considered with regard to genomics patents and the frequent filing of applications is the effect of changing sequence information and priority dates. As the priority date generally lies with the sequence, it is important that the original sequence information be included in each application so that claims can be directed to each sequence. This approach should minimize the effects of intervening prior art, which is often the inventor's own submission of the sequence to public data bases, and should also minimize the effects of intervening applications by competitors. With this approach, the inventors are ensured that they will obtain protection for at least one sequence. Such protection might be sufficient, at least defensively, as long as the claimed sequence is a product (or provides a product) with utility.

File complete specifications and improvements

The first two components of this patent strategy are to file early and to file often. It is thus also important to file a 'complete' specification within one year from the first filing to ensure that the application contains the fullest possible disclosure for both the home country and any foreign filings. Such a 'complete' specification will include all of the disclosures of the various applications filed during the previous year. A provisional patent application in the USA is particularly advantageous in this regard. Although the provisional application(s) must comply with all of the patent requirements (including disclosure requirements) in order to be an effective priority document, the filing date(s) of the provisional application(s) will not determine the term of a US patent – a US patent's term is determined from the filing date of the first regular US application. As a result, the term of a US patent will be equivalent to the term of its corresponding foreign patents.

In addition to filing a complete specification within one year from the filing date of the earliest priority application, it is important that one or more applications (remembering the 'file often' component) be filed for additional developments made before the publication of the application that contains the 'complete' specification. These steps are important, in order to avoid having the publication of the 'complete' specification being used as prior art against the subsequent developments.

This will not be a factor in the USA, however, because a US published application or a published Patent Cooperation Treaty (PCT) application in the English language and designating the USA, will be prior art as of its filing date. In this instance, only potential scientific publications of the initial discoveries by the inventors or others would be prior art against subsequent application(s). This aspect is less important if the inventors only want US patents because of the one-year grace period in the USA and the ability to establish an earlier date of invention with respect to prior art. However, it is important in all other countries. Two patents directed to the *BRCA2* gene[15,16], illustrate the application of these components of the patent strategy. The initial applications for each patent were directed to fragments of the gene with two or more subsequent applications directed to additional gene sequences including, ultimately, the complete gene sequence.

Maximize protection

Several issues must be considered by inventors of specific genomic and research tools.

- The possibility that claims do not cover a therapeutic or diagnostic product or service.
- Claims blocking the use of genomic or research tools might not provide adequate protection, in particular if the genomic or research tool is used before the patent is published.
- The scope of the claims.
- The risk of non-infringing alternatives.
- The question of whether process patents will provide adequate protection.

In view of these issues and the importance of filing applications early, the discoveries must be exploited as much as possible in the patent. It is desirable to try to cover main applications, as well as 'upstream' and 'downstream' applications. Main applications might include ESTs, gene fragments, genes, variants, homologs, paralogs, vectors, probes, pharmaceutical compositions, kits, screening methods, diagnostic methods and so on. Upstream applications might include assays, receptors, ligands, pharmaceutical compositions and so on, and downstream applications might include new comparative methods, second-generation products and so on.

Within this context, it is important to maximize the product initially, that is, composition, provide protection for targets such as ESTs, single-nucleotide polymorphisms (SNPs), genes and proteins. 'Comprising' language should be used in drafting claims for ESTs because, if granted, the claims might cover not only the full-length gene but its uses as well. Second-generation ESTs, which have a definite utility, should be patentable in most jurisdictions. Claims for SNPs will depend on the novelty of the underlying gene. If the gene is novel then claims can be directed to isolated sequences containing the SNPs. If the gene is already known, however, claims should be directed to generic formulae containing the SNPs. To maximize product protection for full-length genes, the claims should include sequences with a certain identity to the gene, sequences that hybridize to it, allelic variants and fragments or functional domains. The use of identity will require that algorithms used to determine the degree of identity be described in the application. The use of hybridization to include other sequences runs the risk of prior art ESTs.

Target discoveries should be used to make therapeutic and/or diagnostic method claims. The key is to protect the therapeutic intervention point that can, in addition, be useful for a deterrent effect. The therapeutic method claims should be based on the modulation of the target and can include antisense and ribozyme molecules. Claims directed to the treatment of a disease are used in the USA, whereas use claims (i.e. Swiss-style claims) are used in Europe and Japan. This might be particularly important for

SNPs. Because it might be easy to design around SNP product claims (that is, the SNP information can be exploited without using the actual DNA sequence), method claims for using the SNP might be more valuable. Such method claims would be based on the association of a SNP with a disease phenotype. These claims might include either diagnostic methods directed to diagnosing the disease or a risk of developing the disease, or to pharmacogenomic methods directed at the prediction of a response to a drug.

Although, as noted above, patents directed to target discoveries often include process claims for screening for drugs, there remains the question of whether such claims could block the sale of drugs identified (or 'made') using the screening method. It is important to attempt to obtain screening claims, which include selecting, manufacturing and formulating steps (i.e. claims directed to methods for formulating pharmaceutical compounds, which include screening steps). It is likely that these claims would have a useful deterrent effect on competitors.

Pursue embodiments

The most important commercial embodiments perceived by either the applicant or corporate partners should be aggressively pursued and prosecuted. Claims to DNA, protein and screening methods should be prosecuted simultaneously if possible. If such prosecution is not possible then the DNA claims will probably be the first to be prosecuted. This aggressive prosecution will ensure that patents will issue as early as possible with respect to the time when the clinical relevance of a target becomes known.

A primary reason for keeping other embodiments on hold is the high cost of pursuing all aspects of an invention at the same time. Obviously, this becomes more crucial for smaller companies and universities than for large multi-nationals. A secondary reason for maintaining other embodiments is that they might become important later and protection can be aggressively pursued at that time. This approach not only conserves finances but also enables the selective targeting of commercial embodiments as they develop.

Review the portfolio

Finally, the patent portfolio should be reviewed periodically to make sure that it reflects the current goals of the business. The portions of the portfolio that no longer fit the goals can be sold or licensed, if desired, to generate additional revenues. The technology of the portions of the portfolio that fit the goals should be reviewed to ensure that all appropriate discoveries are protected. As business objectives can change, no short-term decisions should be made about the elements of the portfolio. Any decisions made should consider the long-range implications and the past analyses of the patent portfolio.

Conclusion

With this strategy in mind, are there any real differences in overall patent strategies between the USA, Europe and Japan? I do not believe so. There might be differences in the subject matter that is patentable (as noted above) and the scope of the claims that might ultimately be determined to be patentable, but the essence of the strategy should be the same. The necessity to be the first to file in the USA in order to be sure that protection is secured in Europe and Japan dictates that applications be filed early for all three. The nature of genomics and research tools, and continuing discoveries dictate that applications be filed frequently and that a complete specification be filed within the one-year priority period to be sure that maximum protection is secured not only for the overall invention but for all of its discoveries, whether concurrent or subsequent.

The fact that applications are currently published in Europe and Japan, and will soon also be published in the USA, dictates that applications for subsequent discoveries be filed before the publication of a first application. The scope of protection must be maximized in the USA, Europe and Japan – maximum product protection should be secured early and claims should be drafted to make best use of the discoveries. In view of the strong competition in this technology, the commercial embodiments must be aggressively pursued in order to block competitors effectively and to ensure an adequate return on investments.

A patent strategy is not static but should evolve as the technology evolves and as the corporate business evolves. The completion of the human genome project and the advent of the analysis of the information generated from this project will have an impact on any strategy for patenting genomics and research tools. An evolving patent strategy must also take into consideration the continual changes in patent law as rendered by statutory changes and court rulings, which can affect the patentability, validity and interpretation of claims and the scope of protection and infringement. Court rulings on the sufficiency of disclosure will also have an impact on any patent strategy. All of these factors must be considered by a corporate business in developing and implementing its patent strategy for genomics and research tools.

In summary, the strategies most suggested and pursued for genomics and research tool patents are to file early, to file often and to maximize protection for the discoveries.

Although there might be differences in the patentable subject matter, which might determine the types and scope of available claims between them, there is no real difference in the strategies for the USA, Europe and Japan.

Statement

The opinions and views expressed in this paper are strictly those of the author and do not reflect the position of the firm or its clients.

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