Patent strategies in molecular diversity

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Introduction

Advocating the property rights of clients is the very essence of what lawyers do. The skill and strategy of that advocacy is an important factor in dictating the results obtained and, specifically, the economic return one can obtain on an intellectual property portfolio. Intellectual property (e.g., patent rights) is a specific type of property which shares legal characteristics with real property, i.e., land ownership. Understanding the similarities and differences between real and intellectual property provides a basis for understanding how it is possible to protect property in the form of inventive methods of chemical synthesis and libraries of compounds in the field of molecular diversity. Researchers may incorrectly assume that it is necessary to isolate a compound with a desired activity from a library to obtain patent protection. However, scores of patents already exist in the field of molecular diversity directed to methods of making libraries, devices used in these methodologies, assay methodologies and on libraries themselves. The following provides a discussion of some of those patents along with an analysis of specific strategies applied to protect the inventions and thereby provide a means for obtaining a lucrative economic return on the research investment.

Real and intellectual property

In a very basic legal sense, real property (succinctly defined as land; however, it includes things that are permanently fixed to land and is technically a right, interest or ownership existing in the soil) is based on ownership of land and intellectual property (broadly speaking, a property right resulting from the physical manifestation of original thought) is based on ownership of ideas (see Table 1). But what does it mean to 'own' land or an idea? Most non-lawyers have little more than a vague idea of what it legally means to 'own' anything and as such are often surprised to find their ownership interest is almost never complete, i.e., absolute (an absolute right in property providing the holder with a complete, unqualified, and unconditional possession, control, dominion, and right of disposition which descends to one's heirs upon death). In a legal sense, ownership interests relate to the degree to which the owner can use and enjoy the property and exclude others from it.

If one owns a home on a piece of land, the right to use and enjoy the land is defined in a deed (a writing signed by the grantor whereby title to realty is transferred) describing rights which are generally sufficient but far from complete. The owner's use of the land is generally limited to a single family home, i.e., the owner cannot use the land to construct a multiple dwelling structure in the form of a multiple story apartment building and

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TABLE I
CHARACTERISTICS OF REAL VERSUS INTELLECTUAL PROPERTY

Characteristic	Real property	Intellectual property
How acquired	Originally discovered and claimed - then conveyed by deed	Originally invented, authored or conceived and protected by obtaining patents, copyrights, trademarks, or maintaining as trade secret
Defined by	Boundary lines - the metes and bounds recited on a deed	Patents by what is claimed and at times what is equivalent thereto
Duration	Defined by the ownership interests of the deed - period of time can be very long or short	Patents valid after issuance and run for 20 years from the filing date with some possibilities to extend
Value relates to	Size and location where others want to be	Breadth of claims and degree to which others want to use what is protected
How protected	Action brought for trespass in state court	Action brought for infringement in federal court

can certainly not use the land as a dump or to build a factory or other business. The owner can generally exclude others from the land but this right to exclude is also limited. Utility companies will generally have 'easements' (a right of use over the property of another) over the land which provide a right to run electric, phone, water, gas, and sewage lines over or under the land. Such easements generally include a right to enter the land to repair and maintain the lines. The ownership interests are also limited in time. Although one can own the property for life and, in general, will the property to an heir, the ability to control ownership into future generations is quite limited. Many jurisdictions have a 'rule against perpetuity', meaning that one cannot convey property beyond the time of lives in being plus 21 years.

Types of intellectual property

Intellectual property (see Table 2) has some basic similarities to real property and noting this is useful in understanding what it means to legally own the products of intellectual creativity. The deed to land is held by the owner and describes the metes and bounds (the boundary lines of land, with their terminal points and angles) of the property. The deed to intellectual property is in the form of a patent (the term 'patent' has a variety of meanings, but is used here to refer to a right, in the U.S., to exclusive manufacture, use, and sale of an invention under Title 35 of the U.S. Code), copyright (a right to exclude others from copying a work of authorship as per Title 17 of the U.S. Code), or trademark (mark of authenticity of being distinguished from the goods or services of others), all of which are issued by the Federal Government.

A trademark is a name, symbol, and/or color (the pink color on insulation was entitled to protection and registration, see Ref. 1) placed on a product to indicate the source of origin of the product. Trademarks can be continually renewed by grants from the Federal Government and Title 15 of the U.S. Code. Although devices and libraries created in the

TABLE 2
TYPES OF INTELLECTUAL PROPERTY COMPARED

Characteristic	Patent	Trademark	Copyright
Time period	Twenty years from filing	Can be perpetual if renewed	Life of author plus 50 years
Legal requirements	Novel, unobvious and fully disclosed	Distinct, not confusingly similar to the mark of another	Original work of authorship
Costs	Generally US$ 5000–20 000	Generally less than US$ 1000	Generally less than US$ 1000
How to obtain	File application fully enabling with disclosure of best mode	File application with mark and use in interstate commerce	Reduce any original work of authorship to tangible medium and file to register
What is protectable	Any new and useful process, machine, manufacture or composition of matter – includes compounds, viruses, cells, or animals but not a method of doing business	Any word, name, phrase, color, symbol or combination thereof but not descriptive or confusingly similar marks	Any original work of authorship reduced to a tangible medium, e.g., books, movies, records, photos, music

field of molecular diversity could be sold under a particular trademark (e.g., DIVERSOlibros™), the trademark would not prevent others from making or selling a similar product provided it was sold under a different name – the difference must be sufficient such that the marks are not 'confusingly similar' to each other. A copyright can be issued to protect works such as writings, music, movies, photos, etc. (any original work of authorship fixed in any tangible medium of expression – see 17 USC §102). The right granted allows the copyright owner to prevent others from copying the particular manner of expression (for example, others may copy the idea of the 'Wizard of Oz' where a girl is separated from her home, has adventures and finds her way home, but may not use the same characters and script to tell the story), but does not prevent others from using the same or equivalent ideas and concepts. For this reason, copyright protection is of little use in protecting the creative output of researchers dealing with the field of molecular diversity. Thus, patents are what is relied on to obtain protection. In some instances, it is possible to obtain protection by maintaining the invention as a trade secret. A trade secret may consist of any formula, pattern, device, or compilation of information which is used in one's business, and which gives one an opportunity to obtain an advantage over competitors who do not know or use it. It may be a formula for a chemical compound, a process of manufacturing, treating or preserving materials, a pattern for a machine or other device, or a list of customers. Others may not illegally take trade secret information, but they may independently develop it and thereafter freely use such information. The characteristics of the main forms of protection are summarized in Table 2 in a generalized and simplified manner.

A U.S. patent is a form of intellectual property which is granted to a patentee inventor, for a limited time, by the Federal Government in exchange for the inventor having created

and disclosed to the world the invention covered by the claims of the patent (see 35 USC §271). Like a deed to real property, a patent to intellectual property allows the owner to exclude others. The land owner can sue for the tort of trespass (any unlawful interference with one's property right) by (i) proving a valid deed is held; and (ii) showing that another has, without the right to do so, trespassed on the land covered by the deed. When (i) and (ii) are proven, a judgement is obtained and generally the trespasser will voluntarily leave the land. However, if the trespasser refuses to leave even after the judgement is obtained, the party obtaining the judgement executes the judgement via the local sheriff who is authorized to use force, if needed, to remove the trespasser. Thus, the owner's right to exclude is fully exercised.

A patentee can sue a trespasser or, in the case of patents, an infringer (in general, one who makes, uses, or sells a patented invention without the authority of a patentee, but see 35 USC §271(a)–(g), which are discussed further below) in a similar manner. The patentee must prove that (i) a valid patent is held; and (ii) the infringer is making, using, or selling that which is covered by a claim of the patent. When (i) and (ii) are proven, a judgement is obtained and the infringer will stop the infringing activity either voluntarily or by being forced to stop by federal marshals.

A deed, as with a patent, can be held invalid for a variety of reasons. (Patents are most often invalidated by showing that the subject matter being patented was known by others before the patentee or was obvious in view of what was known before under two sections of the federal statutes dealing with patents, 35 USC §102 or §103.) However, when a deed to land is held invalid, the ownership rights will end up being held by another, i.e., there is no land without an owner. When a patent is held invalid, it is possible that the ownership rights will go to another such as a prior inventor (such disputes are often handled in a proceeding called an Interference as per 35 USC §146), but generally the rights evaporate and are held by no one. Thus, the public is free to make, use, and sell that which was covered by the patent. A patent does not confer a right to make, use, and sell, only the right to exclude others. If no one has the right to exclude, all are free to make, use, and sell that which was covered by the invalidated patent, provided there is (are) no other patent(s) in place preventing such.

TABLE 3
TYPES OF PATENT CLAIMS

Type	Covered	Not covered	Used when
Product claims	Compounds, libraries of compounds, phage, assay devices	Method of using compounds, more efficient way of making compounds, can still be patented by others	the product is new
Process claims	Methods of making and using compounds	Compounds made by different methods	the process is new and the compound is old
Product-by-process claims	Varies - can cover compounds made by any process, may be limited to process step	Varies depending on whether the compound is new	Best when compound or composition can only be described by the process by which it is made

Deeds and patents are also alike in that the value of each is generally greater if they claim rights to a large area of property. A deed to one square inch of property by itself is of little value in that the owner may not have access to the property and others can avoid trespass easily, e.g., by walking around and not over that square inch. When the claims of a patent are narrowly focussed, others can easily 'design around' that which is claimed and the patent has little or no value. Some deeds cover vast areas but are still of little value. For example, a deed to hundreds of acres in the Antarctica would have little value in that few people want to go on the land. The same is true with respect to patents. A patent which covers a large segment of technology which no one wants to use is of little or no value. Thus, the trick to increasing value (for deeds and patents) is to cover a large area of property located where others want to be. The following explains strategies used to obtain valuable property rights in technologies relating to molecular diversity.

Types of patent claims

The claims of a patent are what describe the metes and bounds of the property owned. If a claim 'reads' on a product, then that product infringes the claim and the patentee can prevent others from making, using, or selling the product (see 35 USC §271 for all rights to exclude afforded by patents). A claim 'reads' on a product if the product includes a component or step which corresponds to each component or step of the claims. The product may have additional components or steps and still infringe. By analogy, one may cross over several different pieces of land every day and be a trespasser on your land if one of the pieces of property traversed is covered by your deed. However, if the claim includes elements or steps which do not correspond to elements or steps of the product, there is no infringement as the claim does not 'read' on the product. Claims are, at times, read under the 'doctrine of equivalents' whereby when there is no literal infringement or 'reading on', infringement is found if the element does substantially the same thing in substantially the same way to obtain substantially the same results.

For example, if you invent a table and claim a horizontal support surface (the table top) and four vertical supports (the four legs), the making of a three-legged table does not infringe the claims – there is nothing for the fourth claimed leg to read on. Thus, to show infringement broad claims which recite the minimum number of elements are more likely to be infringed. However, if a claim is too broad it will be held invalid because it 'reads on' prior art, i.e., it covers previously known and disclosed inventions (one can only get a patent if the invention was not previously known by others or obvious over what was known, see 35 USC §102 and §103). Thus, using the table analogy a claim to a one-legged table would be best in terms of encompassing infringers. However, if one- and two-legged tables were known by others this would invalidate a claim to a one-legged table. A three- or four-legged table claim might be patentable over previously known one- or two-legged tables due to the greater stability provided by the extra leg(s).

There are basically three types of patent claims: (i) product or compound claims; (ii) process or method claims; and (iii) product-by-process claims (see Table 3). The name of each type of claim is self-defining. Product claims cover devices such as robotics [2] which are used in combinatorial chemistry. In addition, these claims can cover a particular compound, group of compounds or even an entire library of compounds [3]. Note that

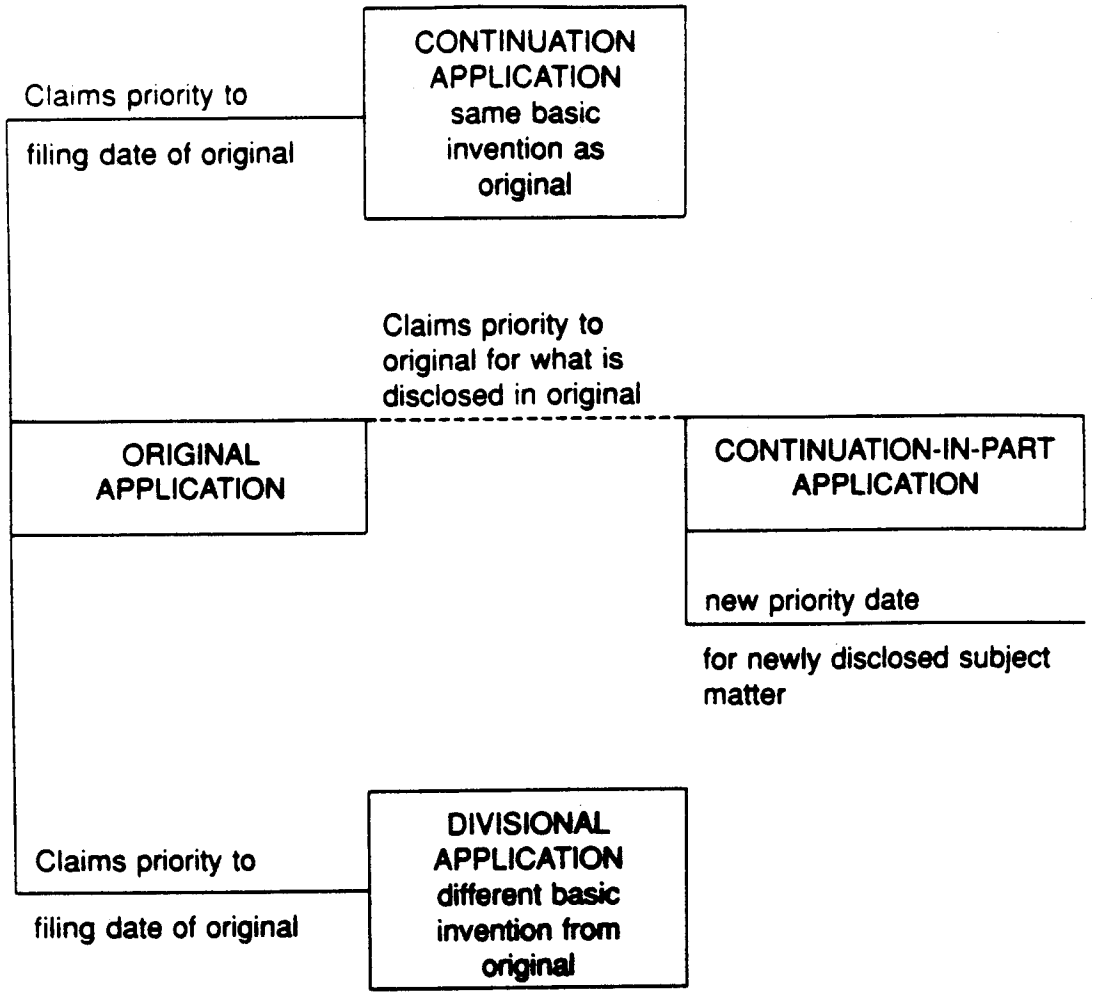


Fig. 1. Patent application and priority dates.

a compound or product claim covers the compound regardless of how it is made. A process claim can cover a series of process steps used in the chemical synthesis of a compound or an inventive method used to produce any product. Note that a process claim may not be limited to producing any particular compound – it covers any process which carries out the claimed steps even though the process might produce a wide range of different products by using different reactants. Product-by-process claims are particularly useful when the product itself can only be described by the process used to make it. A product-by-process claim is subject to different interpretations depending on the circumstances and these are described further below. A 'true' product-by-process claim will cover all products of the type claimed even if produced by process steps different from those recited in the claims [4]. The main types of claims are summarized below.

Process claims

Some of the earlier work in molecular diversity was carried out by Rutter et al. [5] producing large libraries of peptides, i.e., a mixture of peptides which included not just hun-

dreds but tens of thousands and even millions of peptides. The first claims to issue were method claims directed to one specific embodiment whereby activated amino acid reactants were reacted with acceptor amino acid reactants in amounts based on the reaction rate constants. An exemplary method claim from U.S. Patent No. 5 010 175 is the following:

What is claimed is:

'*A method of preparing in the same reaction vessel a mixture of peptides of distinct, unique and different sequences which mixture contains each peptide in retrievable and analyzable amounts and in substantially equal molar amounts, comprising:*

combining and reacting activated amino acids with an acceptor amino acid or peptide wherein the said activated amino acids are provided in concentrations relative to each other based on the relative coupling constants so that the mixture of the peptides resulting from the reaction contains each of the peptides in predictable and defined amounts sufficient for each of the peptides to be retrieved and analyzed.'

The above method claim is broad in scope by covering all methods which use a basic concept of the invention. However, it is narrow in two respects. First, it does not cover peptide libraries made by other methods [6]. Second, it is limited to a specific version of the basic method wherein the reaction product mixture includes each product in 'substantially equal molar amounts'. These limitations were dealt with in related applications as described below. Specifically, the application was filed as a continuation application. (Under 35 USC §120, once a U.S. application is filed additional 'continuation' applications can be filed off it claiming priority back to the filing date of the first filed case, see 37 CFR 1.60.)

The filing of an application establishes a priority date and others wanting to invalidate the patent must be before that date to establish a prior invention. A continuation application has the same priority date as the originally filed parent application (see Fig. 1).

The claims of the continuation application were prosecuted without the limitation regarding equal molar amounts. An issued claim from U.S. Patent No. 5 225 533 reads as follows:

What is claimed is:

'***A method of preparing a mixture of distinct, unique and different peptides in the same vessel, which mixture contains each peptide in retrievable and analyzable amounts, comprising:***

combining and reacting activated amino acids with an acceptor amino acid or peptide wherein the said activated amino acids are provided in concentrations relative to each other based on the relative coupling constants so that the mixture of the peptides resulting from the reaction contains each of the peptides in predictable and defined amounts sufficient for each of the peptides to be retrieved and analyzed.'

The claim from the '533 patent is broader than the claim from the '175 patent. Both claim an inventive method for making a mixture of peptides whereby amino acid reactants are combined with each other based on their relative reaction rate constants. By combin-

ing reactants with each other in proportional amounts based on reaction rate constants, no individual or groups of individual products will dominate the reaction product mixture, thereby drowning out products produced from less reactive amino acid reactants. However, the '533 claim is not limited to producing mixtures wherein each of the components of the mixture is present in substantially equal molar amounts. Thus, the strategy here was to obtain initial protection on a specific embodiment of the invention via the '175 patent which included the 'substantially equal molar' limitation and then to expand the scope via the '533 patent which eliminated that limitation in favor of the phrase 'retrievable and analyzable amounts'.

Both of the above discussed claims are 'method claims' and as such would not cover peptide libraries made by different methods. The value of the claims is determined by their breadth (and these claims are fairly broad) and the degree to which others want to use the method. Methods of synthesis can vary greatly in efficiency and there is often more than one way to make a compound. If there is more than one way to make a compound, everyone will want to use the most efficient method. Thus, if others develop methods which are equivalent or more efficient than the patented method the value of the patent is decreased. This is a difficult problem to deal with when trying to obtain meaningful protection on process inventions. The coverage can be improved at times by (i) contemplating alternative methods of synthesis when filing the application on a primary method; and (ii) defining reactants via general structural formulae rather than specific moieties.

Product claims

At times, an inventive process is applied to produce an inventive product. When this occurs, the product can be patented, thereby making it possible for the inventors to prevent the product from being made by any method. If a patent is obtained on the product, the patent would not prevent others from developing and patenting a more efficient method of synthesis. However, the product patent would dominate the field. More specifically, the holder of the product patent could prevent the holder of the improved method patent from commercializing the new efficient process as it might be applied to making the product via his patented process. In such a situation, both sides recognize the benefit provided by the other and a cross-license agreement is often reached, i.e., each patentee grants the other a license to operate under the other's patent. Both sides may pay the other a royalty based on sales. In general, the product patentee holds a dominant position in the negotiation of the agreement because the product patentee can commercialize the product by using a less efficient method of synthesis but the process patentee cannot commercialize the process unless it can be used to make products not covered by the product patent.

After obtaining the second broader process patent, Rutter et al. were able to obtain claims to a product, i.e., to libraries per se. Prior to the methods of Rutter et al., others made small libraries [7], but not libraries containing thousands of peptides wherein each peptide of the library was present in a relative amount such that it was not drowned out by the presence of other components of the library. Examples of claims to the library per se obtained in U.S. Patent No. 5 266 684 are provided below.

We claim:

'1) A predetermined mixture of peptides containing 8000 or more different peptides of

distinct, unique and different amino acid sequences, wherein the presence of each peptide in the mixture is predetermined, each peptide is present in the mixture in retrievable and analyzable amounts and the mixture includes at least one biologically active peptide in a retrievable and analyzable amount.

(2) A mixture as claimed in claim 1, wherein the mixture contains 160 000 or more different peptides of distinct, unique and different amino acid sequences, each in retrievable and analyzable amounts.

(3) The mixture as claimed in claim 1, wherein the mixture contains 3 200 000 or more different peptides of distinct, unique and different amino acid sequences, each in retrievable and analyzable amounts.

(4) The mixture as claimed in claim 1, wherein the mixture contains 64 000 000 or more different peptides of distinct, unique and different amino acid sequences, each in retrievable and analyzable amounts.'

Claim 1 of the '684 patent indicates that the library contains 8000 or more peptides. Thus, any library containing 8000 or more peptides is covered by the claim regardless of how the library is made provided all the other claim limitations 'read' on the library. The dependent claims 2–4 might, at first, appear broader than the independent claim 1 because they cover larger libraries containing 160 000, 3 200 000 and 64 000 000 peptides. However, dependent claims are always narrower in scope than the independent claims upon which they depend and such is the situation here. A library containing 8000 peptides and having the other limitations of claim 1 would infringe claim 1 but not claim 2, which requires a library of 160 000 or more peptides to be infringed. Referring to the 'table' analogy above, claim 1 is to a one-legged table and claim 2 is to a two-legged table. Thus, claim 2 is narrower than claim 1 because claim 1 covers subject matter not covered by claim 2, i.e., libraries containing 8001–159 999 peptides. A claim to a one-legged table covers both a one-legged and a two-legged table. However, a claim to a two-legged table does not cover a one-legged table.

Product-by-process claims

In addition to claiming libraries via a standard product claim, the '684 patent includes a product-by-process claim as follows.

'(5) A mixture of 8000 or more peptides with distinct, unique and different amino acid sequences, which mixture contains each of the 8000 or more peptides in retrievable and analyzable amounts, the mixture being produced by a process, comprising:

combining and reacting activated amino acids with an acceptor amino acid or peptide wherein the activated amino acids are provided in concentrations relative to each other based on their relative coupling constant so that the mixture of the peptides resulting from the reaction contains reaction product peptides in amounts sufficient for any of the 8000 or more peptides to be retrieved and analyzed and wherein the mixture includes at least one biologically active peptide in a retrievable and analyzable amount.'

A product-by-process claim can be used in three different situations [4] as follows: (i) when the product is new and unobvious, but is not capable of independent definition; (ii) when the product is old or obvious, but the process is new; and (iii) when the product is

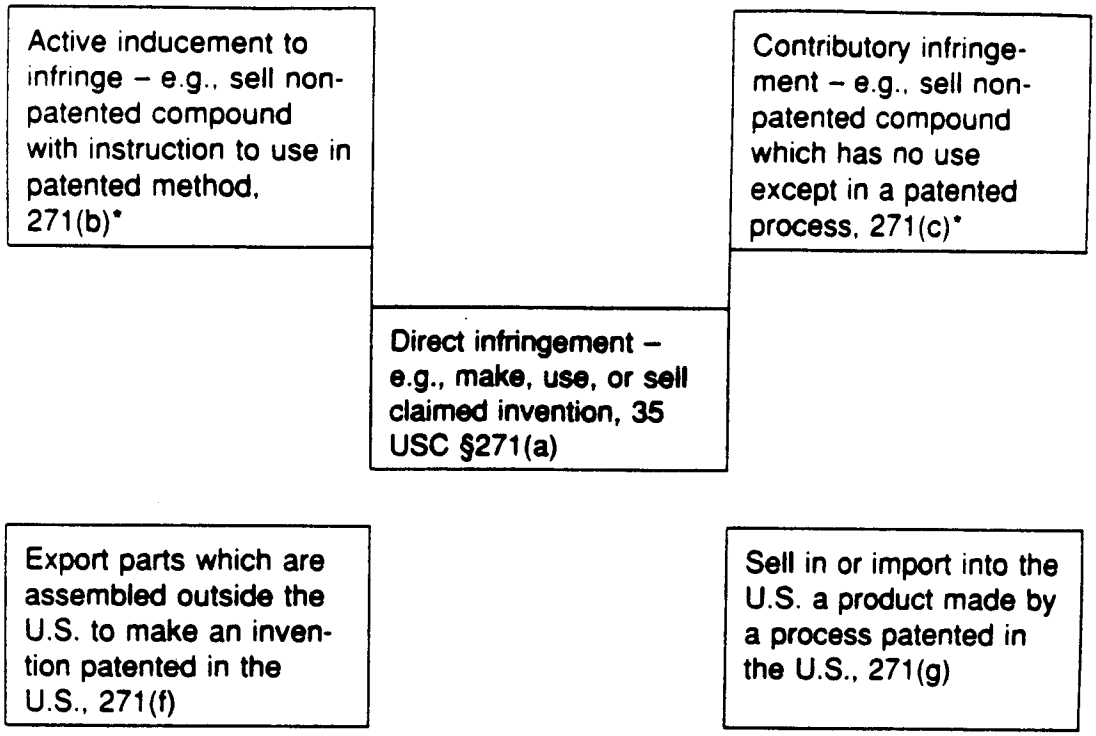
new and unobvious, but has a process-based limitation (e.g., an extruded composition). It is necessary to study the prosecution history of the application resulting in the patent to determine which situations apply. This allows for interpretation of the claim, i.e., determining if the claim covers all such products produced by any process [8] or only products produced using the process steps recited in the claim (see Ref. 4). Because product-by-process claims can be used in a variety of different situations and because they can be interpreted in different ways, such claims can form an important part of a strategy for protecting inventions in the field of molecular diversity.

A strategy of using different types of claims and claims of the same type but different in scope can be applied to robotics [2] used in making peptides and nucleotide sequences, libraries created on the surface of phage [9], diagnostics [10] which use combinatorial libraries or to virtually any invention in the field of molecular diversity – limitations on the type and scope of the claim being dictated by the prior art (under 35 USC §102 and §103 the claim cannot cover that which was previously known or claim subject matter deemed to be obvious in view of that which was previously known) existing at the time of the invention and the extent of disclosure included in the patent application. (A patent application must fully describe and disclose the invention which is claimed. This is referred to as an enablement requirement under 35 USC §112.)

Enforcing patent rights

The vast majority of patents are never litigated. Without litigation, a patent can produce income and value via licensing royalties, encouraging investments, and providing a degree of market exclusivity which makes it possible to obtain a higher profit margin than would be possible without the patent. However, when a patentee is unable to dissuade others believed to be making, using, or selling a product or process covered by the patent, an infringement action can be filed. Understanding the different sections of the statute under which infringement can be filed is useful in understanding how an invention in the field of molecular diversity might be protected.

There are at least five basically different types of infringement (see Fig. 2). (Infringement is covered by 35 USC §271. Although there are more than five sections to the statute and variations and combinations of each type of infringement, an effort at simplification is made here.) (i) Direct infringement (35 USC §271(a); the most common type of infringement) involves making, using, or selling a patented invention. (ii) Active inducement (35 USC §271(b); there must be a direct 271(a) infringer also) to infringe involves taking action which induces another to directly infringe a patent such as selling nonpatented compounds with instructions on how to use them to make a combinatorial library which is patented. (iii) Contributory infringement (35 USC §271(c); the thing sold must have substantially no noninfringing use) involves selling something such as a chemical synthesizer which is not patented but which can only be used for one purpose, which is infringing, such as carrying out a patented process on making a peptide library. (iv) Export/component infringement (35 USC §271(f)) is where one gathers nonpatented components together and exports them out of the U.S. for later assembly into a product which would infringe if made in the U.S. (v) Product of patented process infringement is where one sells a product made by a process patented in the U.S. (35 USC §271(g). This provides broader coverage



*Note that 271(b) and (c) infringement require that someone be a 271(a) direct infringer.

Fig. 2. Types of infringement.

to process claims by allowing a holder of a process patent to sue one who sells a product made by the patented process when that process was carried out outside the U.S.).

By covering inventions via the different types of claims described above and availing oneself of the different types of infringement actions, it is possible to develop a range of strategies for protecting inventions in the field of molecular diversity. It is well known, for example, to use combinatorial libraries to search for one or more active compounds which bind to a given receptor. Claiming the active compounds found would be important, but it might also be useful to claim specific types of libraries likely to contain such compounds and methods of isolating related compounds from the library. Such claims would aid in preventing others from locating and developing related compounds.

Libraries or subgroups of libraries can be products themselves which could be covered by product and/or product-by-process claims. Claims to the library need not describe in detail each or any particular molecule in the library. The claim need only clearly and distinctly claim the boundaries of the library as a whole such that those reading the claim understand when they are infringing – one does not infringe such a claim by making any particular compound but by making the library.

The value of library claims such as those described above in the '684 patent is understood when one considers the 'split resin' methodology [11] which was developed after the 'reaction rate constant' method described above (see 'Process claims'). Using the split resin

method (i) an amino acyl resin is divided into a number of pools; (ii) each pool is reacted with a different amino acid reactant and each reaction is driven to completion; (iii) each of the reaction products obtained in each pool are combined and thereafter steps (i)–(iii) may be repeated any number of times. With each cycle (i.e., repeating steps (i)–(iii)), the number of reaction products obtained increases by a multiple of the number of pools. Thus, using 20 pools for 20 different amino acid reactants the number of reactants increases 20-fold in each cycle. Accordingly, by using six cycles one can create a library of 20^6 or 64 000 000 different peptides. Because each reaction is driven to completion, there is no need to calculate reaction rate constants or to combine reactants with each other proportionally based on reaction rate constants. Thus, the 'split resin' method can obtain the same results as the 'reaction rate constant' method with much less difficulty. However, due to the product claims obtained in the '684 patent, any use of the mixed resin method to make a library containing 8000 or more peptides would directly infringe the product claims as well as the product-by-process claims of the '684 patent. This infringement would exist notwithstanding the patentability of the 'mixed resin' method.

The split resin method was patented via method claims. Those claims would not directly cover a mechanical synthesizer which might be used to carry out the method. However, if the synthesizer did not have a substantial noninfringing use then the sale of the synthesizer would constitute contributory infringement under §271(c), provided it could be shown that at least one purchaser of the synthesizer carried out the claimed method, thereby committing direct infringement under §271(a). Thus, by proceeding under a 271(c) contributory infringement action the patentee can stop the infringement at its source and not be burdened with suing a large number of individual purchasers, i.e., the manufacturer of the synthesizer is sued and not the hundreds of purchasers of the synthesizer who carry out the method and are direct infringers.

Recent developments

Until recently, patents had a term of 17 years from issuance (35 USC §154 prior to 8 June 1995). Allowing the patent term to run from the date of issuance and not from the date of filing of an application for a patent was particularly important for patent applications in technologies where (i) the prosecution period (i.e., the period from application filing to patent issuance) is long; and (ii) the technology continues to retain value many years after the patent issues.

Patent applications filed after 7 June 1995 which issue as a patent will have a term of 20 years (§534 of Pub. L. 103-465 amended 35 USC §154 as of 8 June 1995) from the date of filing of the application, i.e., not a term which runs from the date the patent issues. This creates no problems in some technologies dealing with molecular diversity because (i) the technology is out of date after a short time, e.g., 10 years or less, so that the shorter patent term still provides protection when the technology has value; and/or (ii) the patent application is issued as a patent in 3 years or less from the date of filing, thereby providing a patent term of 17 years or more. The United States Patent Office publishes statistics claiming an application pendency period of about 18 months. However, the number is deceptive in that applications are pending for longer average times in some technologies. Further, the application may go abandoned and be refiled as a continuation

TABLE 4
RECENT PATENT LAW CHANGES

	Old law	New law
Patent term	Seventeen years from issuance	Twenty years from application filing
Patentability under §103	Method needed to be independently patentable over prior methods	Method patentable if product produced is patentable - biotech area only

application several times before it issues. Although the Patent Office would measure each application to get the 18 month member the real pendency period is the total of all the applications, i.e., the time from the first filing to issuance of the last filed continuation application which is generally several times the 18 month period. Applications claiming technologies involving the manipulation of DNA such as in the preparation and use of phage display libraries often take longer than 3 years to prosecute. Thus, the patent will generally have a term of less than 17 years, i.e., 20 years minus the period of prosecution.

Many technologies in the field of molecular diversity are used to find a new chemical entity which is useful as a pharmaceutical drug. Obtaining FDA approval on a new drug can take many years and additional years often go by before the drug is widely accepted and prescribed by doctors. In view of these difficulties, it can easily take 10–15 years before the patent owner receives a return on the research and development investment. Profits being obtained near the end of the patent term are often quite significant, e.g., on the order of one million dollars a day. Thus, any shortening of the patent term can have a significant financial impact on the ability of the patentee to obtain enough profit so that reinvesting in the research and development of another drug appears economically prudent (see Table 4).

Based on the above, it can be understood that some recently enacted legislation could have a negative impact on the biotech industry. However, there have also been positive changes. For example, a recent amendment to 35 USC §103 (35 USC §103(b) amended on 1 November 1995 per Pub. L. 104-41) makes it possible to obtain patent protection on a process for making certain biotech products when the product is patentable even if the process for making it was previously known. One can imagine that a DNA sequence encoding a protein might be patentable even if the protein encoded by the DNA sequence were obvious and therefore unpatentable [12]. As per the new legislation, if the inventor obtains claims to the DNA sequence the inventor is also entitled to claims to methods of making cells containing the DNA sequence and the methods of making the protein expressed by those cells.

Claims directed to methods of making a protein can be quite valuable when combined with claims to the DNA sequence. The claims to the DNA sequence per se could be used under 271(a) against those in the U.S. wishing to make the protein because one would use the claimed sequence to make the protein and be a 271(a) infringer. The claims to the method of making the protein could be used against non-U.S. entities who carried out the process abroad and then imported the protein into the U.S. for sale, constituting 271(g) infringement.

There is a recent case demonstrating how 271(g) can be used to prevent importation of a protein (specifically a hormone) when the patentee only has claims on a process for making a plasmid used to make the hormone [13]. Specifically, in that case Genentech

held a patent on a method of constructing a plasmid which could be placed within a microorganism to produce a human growth hormone. Bio-Technology General Corporation carried out the process covered by Genentech's patent, but did so in Israel in 1983 even prior to the enactment of 35 USC §271(g) but not prior to the issuance of Genentech's patent. Years after making the plasmid via the method covered by Genentech's patent, the human growth hormone made by a cell line containing the plasmid was imported into the United States. Upon importation, Genentech sued Bio-Technology General Corporation under 271(g), claiming that the human growth hormone was 'a product which is made by a process patented in the United States'. The District Court held that the human growth hormone which was imported into the United States was a product which was made by the process patented by Genentech. It was clear that Bio-Technology General Corporation had used the Genentech process of making a plasmid. The plasmid was, of course, an essential part of the overall process of making the human growth hormone. The Appellate Court affirmed the decision of the District Court, pointing out that infringement under 271(g) does not consist of the making of a product by a process patented in the United States (which was done prior to the enactment of 271(g)) but rather the importation, offer to sell, sale, or use of the product made by such a process (which was done after the enactment of 271(g)).

The recent amendment to 35 USC §103 combined with 35 USC §271(g) and the above-discussed Genentech case can be combined to develop some powerful strategies for protecting intellectual property in the field of molecular diversity. Specifically, amendments to 35 USC §103 make it easier to obtain method claims after one has demonstrated that a biotechnology product is patentable. The precedent provided by other recent cases makes it easier to obtain patent protection on certain biotechnology products such as DNA sequences. Product claims to a DNA sequence should prevent others in the United States from using the sequence to make the desired protein product. Such product claims would not prevent others from using the sequence outside the United States to produce the protein product. However, by using the process claims and 271(g), it is possible to prevent the product produced by that patented process from being imported into the United States.

Economic facts

Much of the technology of molecular diversity is directed towards finding chemical compounds which can be developed into pharmaceutically effective drugs. Changes in the law

TABLE 5
ECONOMIC OVERVIEW

Cost/profit	Amount (billion dollars)
Total U.S. health cost	900
Pharmaceutical cost	60
Profit on pharmaceuticals	15
Profit after taxes (net)	7.5

The net profit is 0.83% of total costs. Conclusion: reducing profits on drugs has a negligible effect on reducing total health care costs and could increase long-term cost by reducing the number of new drugs developed.

which make it possible to more readily protect these technologies via patents could have the effect of increasing the price of drugs to consumers in that patents are used to provide market exclusivity and generally increase price and profit. However, as profits increase others are motivated to develop new drugs which provide a benefit to the consumer. Changes in the laws which decrease the term of patents such as by allowing the term to run from the date of the application as opposed to the date of the issuance of the patent could decrease the price of drugs, thereby providing a benefit to the consumer. Specifically, when the patent expires competition enters the market, which generally causes the price to be driven downward. However, a decreased price means a decreased profit for the original developer of the drug, resulting in a decreased motivation to develop new drugs.

When the real economics of health care costs are examined closely, it can be seen that increased drug costs have little effect on increasing overall health costs. Further, providing improved drugs can have a dramatic effect on decreasing health care costs. This issue is often underappreciated by the government and the public at large because prescription drug revenues in the United States exceed 60 billion dollars, which is a large sum. Because the amount of money spent on drugs is so large, it appears that any reduction in drug costs would have a significant effect on reducing health care costs. However, total health care costs in the United States exceed 900 billion dollars. Further, the profits to U.S. drug companies on the sale of drugs are 25% of the revenues or 15 billion dollars before taxes. The 15 billion dollars in profits represent 1.6% of the 900 billion dollars in health care costs and less than that if one considers that federal, state and local taxes return about half of the 15 billion dollars to the government (see Table 5).

Because the profit on drugs sold in the United States represents such a small portion of the overall health care costs (less than 1% after taxes), it can be seen that even a total elimination of the profits on drugs would not have a significant impact on overall health care costs. Further, the elimination or even a substantial reduction of profits on drugs would act as a tremendous disincentive to the development of new drugs. It is generally accepted that 90% or more of all newly developed drugs are developed in the United States. Further, a newly developed highly effective drug could substantially reduce health care costs. Imagine the reduction in health care costs which could be achieved by a new drug which eliminated the need for bypass surgery, cured a particular type of cancer or inactivated HIV replication, thereby curing patients with AIDS. These potential benefits are often overlooked by the government because the U.S. elderly population constitutes about 12% of the population, making up a strong voting block who spend disproportionally large amounts on drugs – just over 25% of total drug expenditures. However, if the true economic picture could be seen it would be understood that increasing patent protection in the field of molecular diversity, and thus pharmaceutical drugs, would be more likely to reduce overall health care costs even if it resulted in larger drug company profits and overall larger expenditures on pharmaceuticals.

Conclusions

Ownership in real and intellectual property can be secured by a number of different legal mechanisms. Those who invent new and useful products and methods can be rewarded with a governmentally granted exclusive right to make, use, and sell the invention.

The purpose of the grant is to promote progress, i.e., encourage others to invent by showing how profitable invention can be. To actually realize a profit, the types of subject matter protectable, types of claims used and, ultimately, the type of infringement actions that might be brought need to be considered in developing an overall strategy.

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