Freedom to Operate: The Law Firm's Approach and Role

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ABSTRACT

In the fields of health and agriculture, it has become increasingly important to understand the role of patent infringement in research, development, and commercial production. If a patented technology is used without permission, the patent holder may have the right to sue the researcher for patent infringement. Many companies routinely analyze the freedom to operate (FTO) of a research project or product, assessing whether it is likely to infringe existing patents or other types of IP rights. Private companies more routinely engage in FTO analysis than public sector research institutions because the infringement risks they face must be directly considered in the calculus of profitability. Public and not-for-profit private institutions also are becoming increasingly aware of the need for better FTO information, but FTO analysis is expensive, and its benefits must be weighed against its costs. This chapter provides an overview of the process, including considerations of when to invest in FTO analysis, and particularly focuses on the law firm's role and perspective.

1. CONCEPTS AND DEFINITIONS

In the fields of health and agriculture, it has become increasingly important to understand the role of patent infringement in research, development, and commercial production. Patenting has become so prevalent in some countries that agriculture and health researchers often use patented technologies daily in the course of their work. If a patented technology is used without permission, the patent holder may have the right to sue the researcher or their employer for patent infringement. Many companies routinely analyze the freedom to operate (FTO) of a research project or product, assessing whether making, using, or selling it is likely to infringe existing patents or other types of IP (intellectual property) rights. The resulting information contributes to a larger risk assessment that may involve a range of options: identifying in-licensing targets, considering the substitution of technologies, deciding to ignore the potential infringement, investing in work-around technologies, or perhaps deciding to abandon the project all together.

Private companies are more likely to engage in FTO analysis because the risks they face must be directly considered in their calculus of profitability. Public and not-for-profit private institutions are becoming increasingly aware of the need for better FTO information. FTO analysis, however, is expensive, and its benefits must be weighed against its costs. Researchers in public institutions, not-for-profit institutions, and in developing countries must consider different factors when weighing the benefits and costs of FTO analysis. In particular, many technologies patented in developed countries are not patented in developing countries. Therefore, institutions making, using, or selling the technologies are not at risk of infringing in those developing countries. However, if a product is *imported* to

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a country where patents on the technologies are in force, then the importer may be infringing in that country.

This chapter and that by Kowalski[1] together provide an overview of the FTO analysis process, including considerations of when (and whether) to invest in this type of analysis. Kowalski discusses FTO analysis from the researcher's perspective, whereas this chapter is particularly focused on the law firm's perspective. In this chapter, we draw from a case study of the E8 promoter. One of many enabling technologies used in the genetic transformation of plants, the E8 promoter provides a concrete example of FTO analysis.

While patents are the most common type of IP right encountered, a thorough FTO analysis will assess *all* types of existing property rights in order to determine the likelihood that the research project or the product being commercialized infringes. As Kowalski[2] and Krattiger,[3] we are also concerned with both intellectual and *tangible property* rights. In biotechnology, tangible property comprises the biological material of the invention: one can physically possess such material. Common examples of tangible property in health and agriculture include cell lines, transgenic mice, germplasm, and plasmids. The transfer of tangible property often occurs under a contract that governs the terms under which the property changes possession but not ownership (commonly called *material transfer agreements,* or MTAs[4]). Unlike IP rights, ownership rights over tangible property do not expire. Tangible property rights provide a further source of protection for certain elements of an invention. Sometimes elements of an invention can be the subject of both types of rights. The use of a gene, for example, may require a license to a patent as well as a material transfer agreement governing possession of the DNA itself.

IP is a category of intangible assets, and includes things such as creative works, inventions, or commercial secrets. Under United States law, IP rights are defined as *exclusionary* rather than affirmative rights. That is, the owner of IP generally has the right to exclude or prevent others from using the intellectual property. The owner can grant permission for use in the form of a license or similar contractual agreement. IP rights are granted by government entities (for example, the U.S. Government or other countries) or by multinational authorities pursuant to international treaties (for example, the European Patent Office [EPO] acting under the European Patent Convention). A grant of IP rights thus confers exclusivity only within the territory controlled by the grantor and only for a limited number of years.

The practice of IP rights in the absence of the owner's permission is defined as infringement. U.S. law provides a number of remedies for infringement, chiefly the award of damages (a monetary award of the amount necessary to fully compensate the IP owner for the harm resulting from infringement) and/or the grant of an injunction (a court order to cease infringing activity or to refrain from commencing such activity). In some cases, additional remedies may apply, such as the award of attorneys' fees and/or the enhancement of damages (doubling or tripling of the award); these additional remedies may be awarded when the act of infringement has been willful.

Because IP rights are exclusionary, the government grant of an IP right, such as a patent, in no way confers an affirmative right to practice the intellectual property. This stands in fundamental contrast to the grant of, for example, a regulatory license by the U.S. Food and Drug Administration (FDA), which does confer the right to sell a new drug or medical device in the U.S. market. Thus, when pursuing a business goal, such as the development and commercialization of a new technology, one must be cognizant of the IP rights of others, because those others may have the right to block or impede progress toward the desired business goal.

FTO is defined as the absence of third-party IP rights that impede progress toward a desired business goal. FTO is also sometimes referred to as *clearance*. As will be discussed below, FTO cannot be conclusively established, but rather should be viewed as an ongoing investigative activity for as long as the corresponding business goal is pursued.

We distinguish the concept of *exclusivity*, as distinct from FTO, defining it as the benefit

conferred by a collection of IP rights amassed by a single owner, that the owner can use to prevent others, such as business competitors, from using a technology. It is possible, for instance, for an institution to have created a high degree of exclusivity for a technology through patenting but still not have FTO because the making, using, selling, or exporting of the technology infringes another's patents.

A collection of IP rights in similar subject matter or a single technology is often referred to as an *IP portfolio*. On a practical level, such IP rights protect the present or future potential market of the owner. The portfolio should be designed so that it corresponds to, and therefore supports, a business goal.

The concepts of exclusivity and FTO must be considered together when assessing the relative risk or desirability of pursuing a particular business goal. When initially formulating the business goal or assessing a new discovery, there may be little to no exclusivity or FTO (or at least knowledge about the status of either parameter) to consider at that time. It is customary to build an IP portfolio in parallel with the process of technology development; however, during the course of development it may be unwise to defer an FTO investigation for too long. As noted above, a particular technology can accrue a high degree of exclusivity in the form of a well-rounded IP portfolio but still suffer from a lack of FTO. The risk associated with further development or commercialization of this technology may lead to remedial steps, such as thoroughly investigating FTO and entering into license agreements to improve FTO status.

Conversely, some technologies, such as those in the public domain, can be commercialized with a relatively low risk of being found to infringe the IP rights of others. However, it is important to understand that public domain technologies are exposed to the full force of market competition through use by others—a product developer cannot shelter them by the exercise of exclusionary IP rights.

Accordingly, in the course of developing a new technology, it is important to consider building the exclusivity of an IP portfolio, while assessing and preserving FTO. That is why this chapter focuses on the process of investigating and monitoring FTO while concurrently building an IP portfolio. Technology that corresponds to business goals and that possesses maximal FTO *and* maximal exclusivity is the most likely to attract and retain investment capital.

It is worth noting that public sector institutions differ fundamentally from private companies in many of the elements discussed here. Consider, for instance, a university's portfolio of relatively early-stage technologies in which the licensee, not the portfolio manager, is commercializing the technology. It is the licensee who assesses risks in relation to a particular business goal and who seeks maximal exclusivity and maximal FTO. For the technology manager, FTO is important partly because blocking patents may make a university technology unmarketable or otherwise limit its future implementation.

In universities, moreover, faculty inventors often respond to a different set of incentives than technology transfer staff. Compared to a private company where incentives are more likely to be aligned around the successful commercialization of products, the bifurcated structure in universities between the production of intellectual property and its management can make it very difficult to coherently assess risk or build an IP portfolio with particular business goals in mind.

Public sector institutions may also pursue goals that are substantially different from those supported by IP management strategies in the private sector. In that sense, the calculus of their risk assessments may differ. For example, an institutional goal may be to preserve broad access to invented technologies or to ensure that new technologies are adopted as broadly as possible. While a public sector institution's use of intellectual property—and therefore its consideration of FTO and exclusivity—to achieve these goals may differ from private commercial companies, a sound understanding of the basic process and characteristics of FTO remains a common critical skill for successful technology management.

2. TYPES OF IP RIGHTS

AS THEY AFFECT FTO

As summarized below, a number of distinct categories of IP rights can be used to build a portfolio. This chapter emphasizes the types of rights typically encountered in the life sciences, such as biotechnology, pharmaceuticals, and medical devices. Naturally, similar issues and opportunities are presented in many fields of technology.

2.1 *Patents and trade secrets*

These first two main types of IP rights are based on the concepts of *inventions* and *know-how*. *Inventions* are the practical, useful aspects of discoveries and are typically embodied in the development of new technology. An invention can be protected by a utility patent if it meets the statutory criteria specified by the relevant government entity. In the United States, patents are granted by the U.S. Patent and Trademark Office (PTO), which is part of the federal government. The criteria include novelty, utility, and nonobviousness. Patents are granted in response to filed applications that provide an adequate written description of the invention, teach how to make and use the invention, and, in particular, point out and distinctly claim the essential elements of the invention in one or more written *claims*. A *patent* is a government grant of the exclusionary right to prevent others from making, using, selling, offering to sell, or importing the invention as claimed. The patent is granted for a limited time: under current United States law, the patent grant expires 20 years from the filing date of the first application disclosing the claimed invention. A *patent portfolio* includes all patent rights, including both issued patents and pending patent applications, that correspond to the invention and its various aspects and uses.

The broader category of *know-how* includes technology and information that may be related to inventions or to their use, marketing, distribution, or sales but is not patentable. Such information, if its proprietary status is maintained, may qualify for trade secret protection. *Trade secrets* are IP rights in unpatented technology and information that confer a competitive advantage to the owner, and are generally unknown. Trade secret status depends on the vigilant preservation of the secret by limiting knowledge of it to those key employees or other workers who have a *need to know* and by using suitable nondisclosure agreements and policies. Examples of trade secrets include ingredients, manufacturing methods, business methods, and customer lists. In the United States, whether information qualifies as a trade secret is determined in accordance with state law. Generally, the applicable law confers on the owner the right to prevent others from copying or pirating the secret. As with patents, the remedies available in the event of the misappropriation of a trade secret include damages and injunctions. However, no remedy is available where the secret is independently discovered by another who acts in good faith and does not engage in unfair business practices. Also, trade secret protection ceases upon publication or other public disclosure of the secret by any party. Thus, while trade secrets may be an important component of the IP portfolio for a particular technology, they may not function as business assets in the same way or to the same degree as patent rights. For example, trade secrets cannot be showcased, as patent rights often are, to attract investment capital.

2.2 *Regulatory rights and licenses*

There are other categories of exclusionary rights besides patents and trade secrets. In the United States, one important additional category includes rights granted by the U.S. Food and Drug Administration (FDA) in accordance with the Federal Food, Drug, and Cosmetics Act. For example, *orphan drug* status provides a seven-year period of exclusivity for a new drug developed to treat a disease or disorder afflicting less than 200,000 individuals in the United States. Once entitlement to orphan drug status is established to the satisfaction of the FDA, the agency generally will refrain from granting any additional regulatory approvals to competing drugs developed for the same disease or condition until the exclusivity period expires. It is not necessary that the drug granted orphan drug status be patentable. Similarly, to encourage the development of new drugs for pediatric use, the FDA may grant a six-month period of *pediatric exclusivity* to the first developer to establish safety and efficacy in

pediatric-patient populations. Finally, to encourage the development of generic drugs upon expiration of patent protection for an innovative drug, the FDA may grant a six-month period of exclusivity to the generic drug developer who is the first to file an *abbreviated new drug application* (ANDA). These regulatory rights and licenses provide important business assets during the commercial lifetime of the technology, rather than at its inception or during the development phase.

2.3 *Copyright*

Copyright is defined as the protection afforded to original works of authorship that are fixed in a tangible (perceivable) medium of expression that can be copied or otherwise reproduced. Copyright exists in literary works, musical works, pictorial works, audiovisual works, software code, and so on. It is important to bear in mind that copyright protects the expression—not the underlying concept or idea. Copyrighted assets that may be relevant to life-science industries include bioinformatics or other software, documents, content posted on Internet Web pages, and advertising and promotional materials. As with patents, copyright is the government grant of the right to exclude or prevent others from making and/or distributing copies of the works and also of the right to prevent others from preparing derivative works. There are limits and exceptions to the scope of this exclusionary right: the owner cannot prevent *fair use*, which encompasses reproduction for such purposes as news reporting, criticism, teaching, and research. Also, under current U.S. law, the copyright lasts only for the life of the author plus 70 years, or in the case of a work made for hire, for the later of 95 years from first publication or 120 years from creation. Remedies for copyright infringement include money damages, injunctions preventing copying or distribution, and court orders impounding or destroying unauthorized copies or the means to create or distribute copies.

2.4 *Corporate identity*

In modern commerce, the principal types of IP rights that protect a technology owner's corporate identity, or its effort to develop goodwill and brand identity, are trademarks, service marks, and top-level domain names on the Internet. A *trademark* is any word, phrase, brief slogan, design, symbol, or logo that identifies the owner as the source of particular commercial goods. In health and agriculture, trademarks can be used to brand products such as plant varieties or drugs. Similarly, a *service mark* identifies the owner as the source of commercial services. As such, trademarks and service marks become important assets during the commercial product lifetime, rather than during the research and development phases. The same is generally true for *top-level domain names (TLDs)*, which may be identical to, or incorporate, the trademark. Under U.S. common law, trademark rights arise via actual commercial use of the mark. Preferably, however, the trademark is registered with the U.S. PTO either upon actual use in interstate commerce, or upon a showing of a bona fide intent to commence such use within a specified time limit. Federal registration provides nationwide rights of enforcement and constructive notice of the mark to infringers. The duration of a trademark right is coextensive with actual use of the mark in commerce. Registration rights are granted for ten-year terms, which may be renewed indefinitely on a showing that the mark remains in actual commercial use. Conversely, a mark can be cancelled from the register if it is shown not to have been continuously used in commerce during the first five years after registration, or at any time if it is shown to have become generically descriptive. Unauthorized reproduction or counterfeiting of the mark, or of a colorable (confusing) imitation thereof, is an act of trademark infringement, as is the unauthorized importation of trademarked goods. Remedies include the grant of a permanent injunction against copying, recovery of the infringer's profits, money damages, and costs. Infringing goods can be impounded and/or destroyed. If the infringing mark is a counterfeit, treble damages and attorneys' fees are available. In the case of a TLD, the remedy may be limited to the transfer of the registration to the rightful owner.

2.5 *Plant breeders' rights*

Plant breeders' rights (PBRs) protect plant varieties that are deemed new, uniform, stable, and distinct against unauthorized sale for replanting. PBRs do not generally prohibit the use of germplasm as breeding stock for creating new varieties. However, an exception to this was included in the 1991 version of the International Union for the Protection of New Varieties of Plants, commonly known by its French acronym UPOV. It prohibits the breeding of a variety *essentially derived* from a protected parent.[5] In the United States, *plant variety protection certificates* (PVPCs) confer protection against the use of sexually propagated seed germplasm. PVPCs are administered by the U.S. Department of Agriculture (USDA) under the legal authority of the Plant Variety Protection Act of 1970.

The foregoing is not an exhaustive list of the types of IP rights that may be relevant to a particular technology or product. For example, design patents may protect an attractive or distinctive original design of a useful article, such as a medical or diagnostic device. In the field of agricultural biotechnology, although plants are generally protected by utility patent rights, either *plant patents*—which in the United States grant protection from unauthorized use of most clonally propagated plants—or PVPCs may be obtained in addition to or in lieu of utility patent rights.

3. SUBJECT MATTER OF THE FTO

The first step in conducting an FTO investigation is to define what is to be searched. How precisely the subject matter can be defined will depend largely on the developmental stage of the product or other technology, as well as the nature of the technology itself. For example, a product candidate ready to enter preclinical development requires a more substantial search than a newly discovered gene or biological pathway. In addition, research tools and platform technologies may present unique restrictions on the scope of an FTO search. For example, the search may be limited to an anticipated field of use, or a full search of all uses may be required. Manufacturing technology and methods of use likewise may permit more or less precise descriptions of the subject matter to be searched. Manufacturing typically involves a number of different technologies, such as gene-expression vectors and host cells, as well as a number of different process steps. Each of these technologies may require an individual search, or the search may center on specific combinations of technologies and/or processes. Methods of use may be broadly or narrowly defined; related fields and collateral uses (for example, off-label uses of a therapeutic agent) may also require searching. In addition, the country or countries to search in must be identified. These should include any countries in which the technologies are likely to be made, used, or sold, as well as any countries intended as destinations for export. In general, the subject matter to be searched should be defined as precisely as circumstances permit. When a search is revisited or updated, care should be taken to refine the definition of the subject matter to be searched.

4. WHEN TO CONDUCT AN FTO SEARCH

Prudence must be the watchword guiding the decision of when to conduct an initial or updated FTO search. The decision depends, as a practical matter, on the nature of the risks involved and the level of risk tolerance acceptable to the client. The following is a brief survey of typical considerations that may guide the decision to engage in an FTO investigation as well as how such an investigation should be defined.

4.1 *Business goals*

One particularly useful rule of thumb in determining whether to conduct an FTO search is to review and rank the relative importance of an entity's business goals. This should be done by the decision maker in consultation with counsel. For each business goal, counsel must ask the decision maker whether they could *walk away* from that goal, that is, cease all activities in pursuit of that goal. This assessment is dictated by the availability of permanent injunction as a remedy for infringement of a number of different types of IP rights, such as patents, trademarks, and copyrights. Several subsidiary considerations further guide this analysis.

First, it has become clear that, under United States law, there is effectively no *research exemption*: the decision in *Madey v. Duke* indicates that exploratory or basic research may constitute patent infringement. So far, commercial companies have not sued universities for the infringement of patents used by their faculty in research.[6] Indeed, a commercial company's decision to turn a blind eye toward infringement in the public sector makes some economic sense. Were a patent owner to sue and win a patent litigation case against a university, the patentee would be titled to injunctive relief and damages, that, for the typical use of patented technologies in basic research, would likely be negligible and not worthy of multimillion dollar patent litigation. However, universities who wish to promote the further development and eventually the commercialization of their faculty's research may want to pay increasing attention to FTO issues so that they can understand how their technologies are situated with regard to other patents in the field and how they can reduce potential future impediments to commercialization.

There is, however, a *safe harbor* exemption for research and development relating to the submission of applications for regulatory approval by the FDA, including both clinical and preclinical studies. The scope and limits of this safe harbor have not been conclusively established, necessitating a case-by-case analysis. Also, many developed countries have similar laws governing whether basic research and research related to the approval of new drugs is exempted from patent infringement. The scope and precision of laws on this point may differ significantly from country to country, and a detailed discussion is beyond the scope of this chapter.

Second, and in view of the above, one must consider the geographic scope of the market to be served by the business goal under consideration. Since IP rights are granted by governments and are territorial in nature, an FTO investigation should apply the laws of the country or countries in which activities are undertaken in pursuit of the business goal. For example, all research, development, and manufacture may take place in the United States, but the commercial market may include Europe as well as the United States. In other situations, the inverse may be true. The corresponding FTO investigations should identify and assess third-party patent rights in both the United States and Europe. In the case of a worldwide market, cost and a pragmatic assessment of risk may dictate that the FTO assessment be restricted to major markets.

Third, it is important to consider how much has been invested in the business goal to date. A significant investment, or an investment representing a significant portion of total business assets, heightens the need for an FTO search. This principle is illustrated below in the context of a biotechnology or a pharmaceutical for human healthcare. Another approach, suitable to assessing FTO for a research tool or platform technology, is to determine whether use of the technology is limited to a specific (and minor) project. If the technology will be relied upon broadly, or will underpin an important long-term business goal, an FTO search should be considered early.

A related consideration is whether the early establishment and monitoring of FTO will increase the attractiveness of the business goal to potential investors. Venture capital investors and large institutional investors tend to be quite sophisticated and keenly interested in the IP risks pertaining to a technology or business plan of interest. More recently, a well-formulated IP strategy is a requirement for funding agencies that, in addition to supporting research, are dedicated to ensure the prompt dissemination of a project's outcome.

4.2 *Risk of IP infringement litigation*

Another rule of thumb is equally important. Counsel and the decision maker should assess together whether the client can tolerate the risk of litigation. Risk tolerance varies with government oversight and regulations, management style, and the nature of business activities, but is also closely tied to financial resources, including the availability and scope of relevant insurance. When assessing the risk and consequences of infringement litigation, one must bear in mind that, at least in the United States and Europe, the cost of defense is significant. Also, at least in the United States and the United Kingdom, damages awards

for patent infringement tend to vary from large to quite large. Legal costs and damages, taken together, can figure in the tens of millions to the hundreds of millions of U.S. dollars.

As mentioned previously, another significant risk of infringement litigation is that a court will issue a permanent injunction, for example, ordering the client to cease its infringing activities or, under certain circumstances, ordering the seizure, impoundment, and/or destruction of infringing goods. Thus, the risk assessment must take into account the value of lost business opportunities. There may be other risks consequential to the initial infringement liability, such as shareholders lawsuits and investigation and/or enforcement actions by regulatory authorities (for example, the U.S. Securities and Exchange Commission [SEC][7]).

It must be noted, however, that infringement litigation is also costly to the plaintiff and may not be pursued when the unauthorized use of the technology does not threaten the patent holder's business goals. The use of patented technologies in the course of academic research in the United States, for instance, has been shown to constitute infringement, but infringement lawsuits against academic researchers are likely to provide little benefit to the patent holder either through injunction or through the recovering of damages. Examining the economic and legal rationales for infringement litigation may be particularly important for assessing the risk of infringement litigation by researchers in public and not-for-profit institutions and in developing countries.

4.3 *Level of investment*

A third useful framework for deciding when to conduct an FTO search is to determine what business decisions should trigger the search. It will be fairly straightforward to identify the types of decisions that would significantly increase resource commitments to a specific business goal. Such discontinuities in business strategy or financial investment should signal the need for an initial or updated FTO search. Indeed, many companies have made projects pass a series of increasingly rigorous FTO studies during the course of development. A sampling of the changes in investment that may merit new or updated FTO studies in the development of a novel biologic or pharmaceutical drug are illustrated in Box 1. Analogous investment changes that may warrant an FTO analysis also exist in other fields, such as agricultural and industrial biotechnology.

5. SCOPE OF THE TYPICAL FTO INVESTIGATION

A typical FTO search canvasses all reasonably available sources that are likely to reveal relevant third-party IP rights. For the most part, these are computerized databases and search engines capable of surveying publicly accessible patent, technical, and commercial literature. Issued patents, published patent applications, and scientific/technical publications, as well as databases of meeting presentations and grant awards, can be searched using keywords, investigators' names, assignee/owner names, and subject-matter classifications. Biological sequence databases, including both nucleic acid and protein sequences, can be searched using a query sequence. Patent assignment branch records should be searched to reveal the names of real parties in interest, as well as transfers of ownership. Patent annuity and maintenance-fee records should be searched to verify that patents identified as relevant are in fact still in force. On the commercial front, the SEC filings of identified assignee/owner businesses that are publicly traded can be searched on the electronic data gathering, analysis, and retrieval system (EDGAR)[8]. The filings of interest include companies' quarterly (8-K) and annual (10-K) reports of progress toward their business goals, which include self-assessments of risk. A search of the records of known competitors may reveal common threats to FTO status, such as third-party IP rights in broad classes of molecules (for example, fusion proteins) or manufacturing technologies. When appropriate, press releases, industry-specific news reports, and stock analysts' reports also should be investigated.

5.1 *"Level one" FTO investigation*

As mentioned above, not every FTO investigation merits the same scope or depth of search.

Box 1: Changes in Investment Meriting an FTO Analysis of a New Drug or Biologic

Selection of a druggable target

Exploratory research into a specific biological pathway may reveal one or more genes or proteins that appear to be a suitable site for intervening in a disease process or other metabolic process. A *druggable* target is a molecule identified as pivotal to a biological process, with a structural feature such as a cleft for which a pharmacophore can be identified or designed. In many cases, IP rights encompassing the use of the target or compositions of matter corresponding to all of the target or specific parts of the target may exist. Universities and research institutions frequently own such IP rights.

Screening/ research tool technology

A number of companies have developed business models based on providing tools and services to the research community, and these may be aggressively protected by IP rights. Affymetrics, for example, markets and sells nucleic acid microarray chips. The Harvard oncomouse, commercially available from DuPont, is another example.

Identification of a lead compound

The selection of a lead compound typically represents the transition from research to development. It is axiomatic that the structure of a lead compound, one incorporating a successful pharmacophore, cannot reliably be predicted based on knowledge of the target. Thus, the lead compound and the structural class to which it belongs represent both new opportunities for developing an IP portfolio and new risks in light of which FTO should be established before committing resources to a development-phase project. Both specific and general features of the lead compound should be investigated. For example, IP rights may be found to cover humanized antibodies or different types of fusion proteins. The same considerations apply to any back-up compound.

Preclinical development

The commencement of preclinical development means both a significant rise in the level of financial commitment and the beginning of the *safe harbor* from patent infringement. Here, activities focus on the development of data to be included in an investigational new drug (IND) submission to the FDA. Despite the safe harbor, this step represents a formal commitment to develop a new drug or biologic for eventual commercial use. Thus, from the investment standpoint, it is a critically important stage at which to conduct a thorough FTO search or update and refine a prior search. Also, at this stage, many ancillary aspects of commercialization may be established beyond the structure of the drug candidate, such as its formulation or dosage, its primary commercial indication for use, and basic manufacturing techniques.

Selection of manufacturing technology

In many instances, the manufacturing technology needed to support commercial scale production of a new drug will differ from that practiced at the research or even developmental stage. Because of the magnitude of resource commitment required for manufacturing, many companies have patented successful manufacturing techniques broadly. One example would be the patenting of a particular type of chromatography resin to purify a particular class of molecules (for example, humanized antibodies). Another example would be the type of host cell or a formulation found to enhance shelf life or solubility.

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Box 1 (continued)

Selection of a clinical indication(s)	A main or primary clinical indication for the new drug or biologic may have been selected based on an understanding of the target and its mechanism of action. As development progresses, however, additional indications may become apparent, as may additional channels of commercialization (for example, neurologists may find the drug attractive for one disease, while gastroenterologists may perceive its value for another distinct disease). Each distinct clinical indication may attract its own competitors, dictating the need for corresponding FTO studies.
IND Submission	An IND application is the document the FDA uses to decide whether to allow human trials of a new drug or biologic agent. Readiness to submit an IND and, even more so, holding an approved IND represent a critical achievement in the business life-cycle. The interest of investors and potential corporate partners or acquirers is piqued, and the value of a business is significantly enhanced. It is particularly important at this juncture to establish the feasibility of the business goals corresponding to the drug development project. Indeed, a number of pharmaceutical companies treat the FTO investigation conducted at this juncture as the *go/no-go* decision on commercialization.
Pivotal clinical trial	A pivotal clinical trial is one that can generate statistically sound data that the FDA can use to decide whether to approve a drug for commercial sale. Depending on the clinical indication, such a trial may take from one to five years, and may involve from tens to thousands of patients. Initiating and conducting such a trial often represents the single largest investment made during the course of commercialization. In addition, starting such a trial signals a commitment to particular drug compositions, formulations, methods of manufacture, and methods of administration and use. This commitment alerts third-party IP rights holders to the value of their IP, raising the cost of establishing FTO by entering into license agreements or avoiding adverse IP rights by *designing around* them.
NDA/BLA submission	The new drug application (NDA) or biologics license application (BLA) is the dossier submitted to the FDA for its decision on commercial approval of a new drug or biologic agent. FDA approval, which typically takes from two to four years, signals the end of the *safe harbor* from patent infringement. Thus, the period of NDA/BLA pendency represents the last stage at which any remaining FTO issues may be resolved without exposure to infringement litigation.
Commercial launch	This is the commencement of actual commercial activity, the stage at which a company is fully vulnerable to charges of IP rights infringement. Prudence dictates that FTO must be established prior to this stage and that periodic monitoring be conducted to ensure preservation of FTO throughout the product's lifetime.

Exploratory-stage research, or consideration of a new business goal, may require no more than an overview and risk identification. The question to be answered is whether there are any so-called *blocking patents* that would preclude pursuing the new goal. This is called a "Level One" FTO study to distinguish it from more in-depth analyses. The Level One study assesses only public information, typically in the following two categories:

- **Patent database searches.** Keyword, surname, business name, and sequence searches of patent databases are conducted to reveal relevant patents and published applications (which are potential future risks).
- **Patent ownership and status searches.** Surname and business/entity name searches of assignment branch records are conducted to reveal ownership interests, transfers of ownership, and other recorded rights affecting ownership. If deemed prudent, secretary of state records may also be searched to reveal any transfers or liens that may not have been recorded at the federal level. Searches of relevant annuity/maintenance-fee databases are conducted to reveal whether any of the identified patent risks have lapsed for nonpayment.

5.2 *"Level Two" FTO investigation*

There are many ways to design and implement more in-depth FTO searches. The nature of each search is dictated both by the precise definition of the subject matter to be searched and by the decision maker's desired degree of risk characterization. Both considerations rest, in turn, on the significance of the business goal and the amount of resources required to achieve it.

A typical "Level Two" FTO investigation is considerably more sophisticated than a Level One, yet still only requires access to public information. Assessing nonpublic information requires either cooperation among the relevant parties (for example, IP due diligence in support of a business alliance) or court order (such as during the discovery phase of infringement litigation). Both are beyond the scope of this chapter.

Patent database searches are conducted as described in the Level One investigation, but the analysis conducted on this raw data goes beyond mere identifying potential *blocking* patents. Instead, the patent rights are evaluated substantively to construct a *patent landscape* in which the patent claims are grouped by subject matter. For example, one group may encompass expression vectors and be subgrouped according to the type of vector. Another may encompass host cells, including specific types of host cells and their culture methods. Yet another group may encompass the structural class to which the drug of interest belongs. For example, all patent rights on fusion proteins may be grouped together, with sub-groups defined according to the protein class of interest (for example, receptor-Ig fusion proteins). The groupings can be configured to most effectively educate the business decision maker about how to proceed.

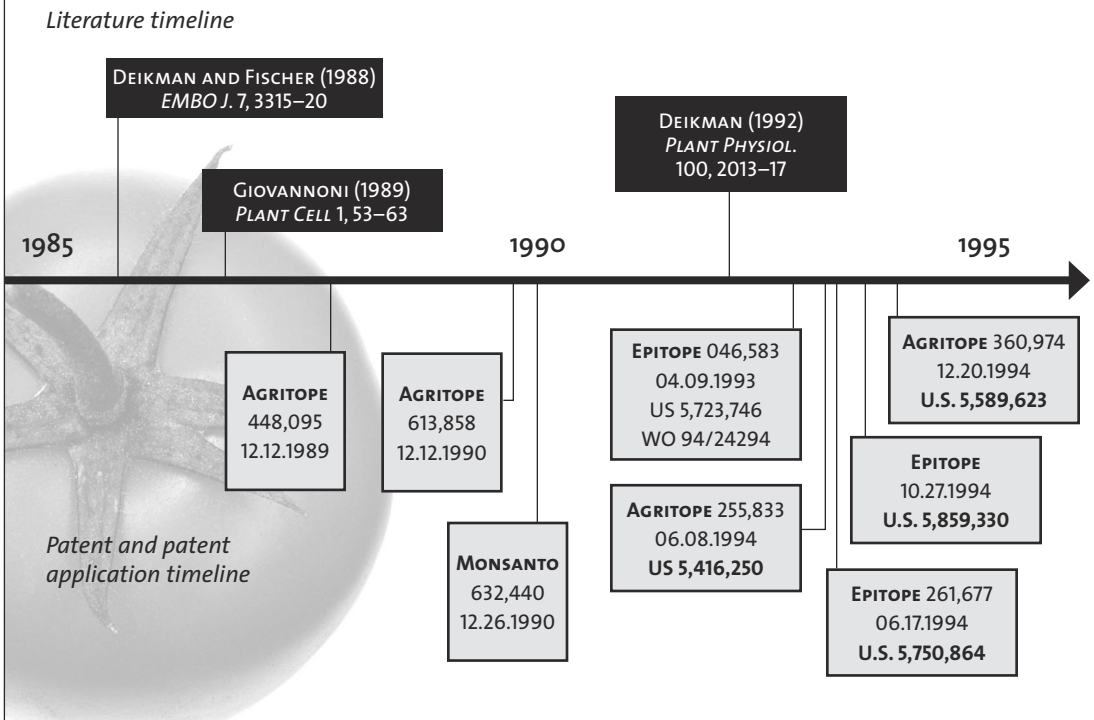
Another very informative way to analyze the search results is to construct a timeline of patents on similar or overlapping subject matter. Ordering the patents and published applications according to their *priority dates* (also known as *effective filing dates*) reveals important relationships. For example, it reveals which patents are *prior art* against newer patents. Since patents may only be granted if the claims are both novel and nonobvious over the prior art, this analysis reveals the relative dominance of earlier, broader patents over later, narrower patents. There are many circumstances in which broadly and narrowly defined claims covering the same subject matter can coexist and be owned by different parties. Analyzing the priority timeline will reveal whether some patents should be licensed or designed around by developing alternative technology. This analysis will also reveal which parties possess more leverage to seek higher license fees. Including published applications in the timeline enables the astute decision maker to make educated guesses about the scope of claims likely to issue from applications filed later. Finally, it provides insight into possible interferences. Unique to U.S. patent law, an *interference* is an administrative proceeding before the Board of Patent Appeals and Interferences, in which two or more parties claiming the same subject matter in separate patent applications engage in a contest to determine who was the first

to invent. The procedural rules are strict, and the winner is awarded the patent. Figure 1 in the case study below illustrates a typical patent-priority timeline.

Scientific and patent literature, including patents and patent applications, illustrate the existing prior art at the time that related patent applications were filed. The priority dates of each patent and patent application relative to the publications dates of the main scientific literature are shown.

The analysis of priority claims in published patent rights also reveal *family* relationships among different patents and published applications. *Patent families* include both vertical and horizontal relationships. A vertical or lineage relationship arises when a later patent application claims the benefit of an earlier, related application that names the same inventor (or at least one common inventor, in the case of joint inventors). If the *specification* (text portion of the application) is identical to the earlier application, but the claims cover different subject matter, the later application is called a *continuation* or a *divisional*. If the specification has been edited to disclose more or less information, and corresponding changes have been made in the claims, the later application is called a *continuation in part*. Horizontal relationships arise in *foreign filings*, counterparts of the original application filed in other countries or common patent territories. Such foreign filings are made under bilateral or regional treaties in which two or more governments agree to reciprocally recognize the priority of applications filed in each others' territories. The main vehicle for generating horizontal families of counterpart applications is the Patent Cooperation Treaty (PCT). The PCT provides a preliminary *clearinghouse* in which the claims are searched, and optionally examined, by a single examining authority. Both

Figure 1: Timeline of Tomato E8 Scientific Publications and Patents



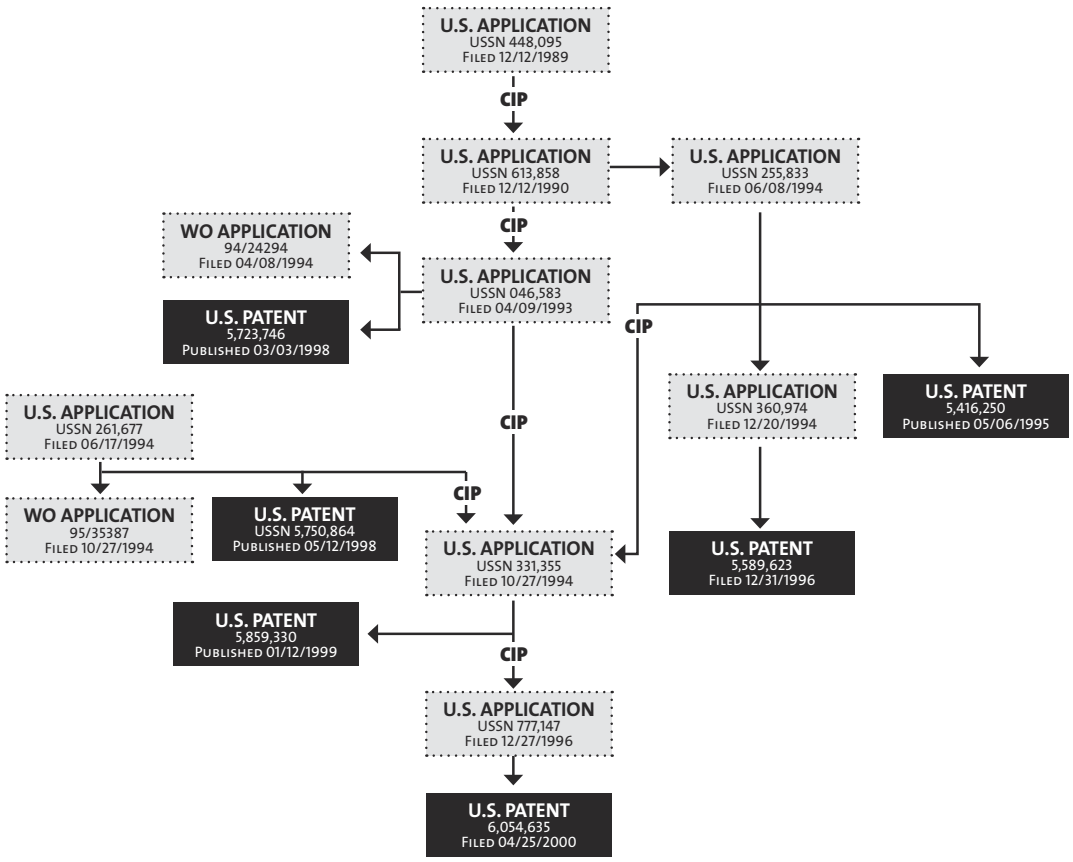
Scientific and patent literature, including patents and patent applications, illustrate the existing prior art at the time that related patent applications were filed. The priority dates of each patent and patent application relative to the publication dates of the main scientific literature are shown.

the PCT examination report and the PCT search report are publicly available. Figure 2 in the case study below provides an illustration of patent family relationships.

Very often, the foregoing analyses reveal a subset of identified patent rights that require close analysis, including advice to the decision maker about the scope of the patent claims. This type of analysis is known as *claim construction*. It requires counsel to obtain and evaluate the patent file histories. The *file history* (or prosecution history) is the written record of negotiations between the patent applicant and the examiner. The patent specification (text portion) typically does not change during prosecution; however, the claim language does change, sometimes quite dramatically. For example, the examiner may require that the claims be divided into subsets, which are then prosecuted separately in divisional applications. Other changes in claim language arise from the need to conform to patentability requirements, such as enablement, written description, clarity, novelty, and nonobviousness. Even where the claims have not been amended, the patent applicant may have made remarks that define the scope of the claim or that disclaim a broad interpretation. Such remarks are referred to as *file wrapper estoppel* or *prosecution history estoppel* because the patentee is not allowed to assert a broader claim scope when enforcing the resulting patent.

In the United States, prosecution history analysis is restricted to the histories of issued patents and published applications, since the files of provisional and unpublished applications are

Figure 2. The Epitope/Agritope Patent Family



confidential by law. In most cases, the file histories of foreign counterpart applications are available to the public. Thus, one can obtain insight into the potential scope of patentable claims by obtaining and analyzing the file histories of one or more counterpart applications in a patent family. European prosecution histories are available electronically as .pdf files. Australian histories can also be obtained and are often useful because the pace of examination in Australia is frequently more rapid than it is in other PCT member states. Each foreign counterpart application is examined in accordance with the granting country's patent law, so one must expect to encounter more or less nuanced differences in the scope and format of patentable claims.

In addition to analyzing prosecution histories, it is necessary to check the appropriate patent litigation databases to determine if any patents of interest have been held invalid or unenforceable. The PTO Web site should also be checked for information on whether an interference has been declared involving a patent of interest. The interference proceedings are not public information, but the final decisions of the Board of Patent Appeals and Interferences are publicly posted. Similarly, the records of foreign patent offices should be checked to determine whether any newly-granted patents have been the subject of patent oppositions. An opposition is an administrative proceeding in which any member of the public adversely affected by the patent grant may file arguments urging that the patent should not have been granted, that is, it fails to comply with the grantor's laws on patentability. Europe and Australia are among the countries that permit the filing of oppositions within a specified time period following the patent grant. The record of opposition proceedings in each country is publicly available.

Finally, a prudent and thorough FTO investigation includes searches of business and news records as well as of patent records. General and industry-specific news reports may reveal the names of business or nonprofit IP holders not revealed through the patent database searches. They may also provide useful overviews on the state of the art or the competitive marketplace. If available, stock analysts' reports on an industry sector or an individual business are particularly helpful. Such reports often provide independent, expert assessments of business risk, including IP risks. As mentioned earlier, the annual report or SEC filings of an IP rights holder provides useful self-assessments of risk and competition. Perusing the patentee's Web site and relevant press releases will often reveal whether the patent rights in question correlate to a stated business goal. Such information provides the decision maker with valuable insight into both the business model of the patentee and the importance—and therefore value—that the patentee places on the patent rights of interest. For example, a university or nonprofit organization may have a stated policy of licensing its IP rights in order to pursue its mission of advancing public knowledge or providing public benefit. Similarly, research tool companies have adopted business models that rely on broad licensing of their IP rights. In contrast, innovator drug companies and biotech companies may be motivated to preserve their exclusionary rights, such that licenses may not be available, or offered only on unfavorable terms.

5.3 *Limitations*

It is imperative for the decision maker to bear in mind, when considering the results of any FTO investigation or clearance search provided by counsel, that such searches are, by their very nature, limited. First, the search is limited in time. New patents may have issued since FTO was last analyzed, and it is for this reason that periodic updates must be considered. Second, the search is limited to publicly accessible information. It is impossible to identify all of the new inventions made in the field of interest or to characterize the trade-secret rights claimed by competitors or other business entities. Similarly, no FTO search can identify or analyze unpublished patent applications. This category includes United States provisional patent applications, as well as utility applications that are less than 18 months old (as measured from the priority date). Under current United States law, older utility applications also may not be published if the applicant has requested nonpublication and disclaimed the right

to file foreign counterpart applications. Also, as mentioned above, the file histories of unpublished U.S. applications are not available to the public. For these reasons, an FTO investigation may need to be updated regularly. If desired, an automated, computer-based monitor may be instituted to alert counsel of new patent information as soon as it becomes publicly available.

Business information also may not be available. A company's business goals and the status of its research and development projects, for example, may not be publicly disclosed. Similarly, information about the competitive risks perceived by the company may not be publicly available. While lawsuits are a matter of public record once filed, invitations to license a patent, threats of litigation, licensing negotiations, and settlement discussions are usually not in the public record. Corporate documents, such as contracts affecting the ownership of intellectual property (for example, assignments, security interests, joint development agreements, service contracts) also are usually not public records. Similarly, contracts affecting the use of IP rights (for example, licenses, settlements, options, material transfer agreements, confidentiality agreements, employment agreements, consulting agreements, noncompetition agreements, service contracts) are usually not public records. Business information influencing the results or interpretation of an FTO study may not be revealed until a due diligence investigation is carried out as part of a license negotiation, or until the discovery phase of a patent infringement suit commences. In certain circumstances, however, the existence of a corporate document that affects ownership or use of IP rights *material* to a publicly traded company's business may be revealed in the company's SEC filings. A document is considered *material* if it affects the value of the company's stock.

Another key area that usually cannot be explored when using only publicly available information is whether there are any adverse claims to inventorship of third-party patent rights. Increasingly, inventorship disputes are being considered in litigation and other adversary proceedings as a way to obtain a license from a newly added, sympathetic co-patentee. As with nonpublic business information, the existence of possible inventorship claims is often not revealed until a licensing due diligence investigation is carried out with the consent of the patentee or the discovery phase of litigation commences.

6. THE PRODUCT OF AN FTO INVESTIGATION

The product of an FTO investigation conducted by a law firm or an in-house attorney and communicated to the decision maker is uniformly recognized under U.S. state law as being *attorney-client privileged information*, and depending on the circumstances may also fall under the *work product privilege*. The results retain their privileged status as long as the client (who holds the privilege) chooses not to reveal the information to others, or it is not inadvertently disclosed. The attorney-client privilege applies to advice regarding IP rights in most European countries as well as in the United States. It is important to keep in mind, however, that in some countries patent professionals are not attorneys; thus the degree of protection afforded to the results of an FTO investigation may vary and should be established in advance. Switzerland, for example, does not recognize privilege in the communications between a patent practitioner and a client, although it does so between an attorney and a client.

In many circumstances, for example, where a Level One FTO investigation is all that is needed, the results of the investigation may simply be the oral advice of counsel to the decision maker. Depending on the purpose of the FTO investigation, or where a more-detailed Level Two investigation has been carried out, counsel may provide a written report to the decision maker. Typically, the report includes brief statements of the scope of the search, as well as a listing of the search strategies used (for example, keywords, sequences, assignee names). The report also includes a listing of the identified third-party IP risks. A written report of the identified risks is usually brief and carefully worded because of the potential for such commentary to function as admissions against interest of the client, if the attorney-client or work product privilege is lost or waived.

The most important feature of any document reporting the results of an IP FTO investigation is that it is a *living document*—it should be updated as new information comes to light through a monitor or through a regular schedule agreed to between counsel and the decision maker. The decision maker should understand that decisions may have to be modified or reconsidered in light of updated information about changes in the nature of the IP risks being monitored, their status, or newly emerging intellectual property. This process should continue for as long as the business goal is pursued.

7. IP RISK MANAGEMENT STRATEGIES

The process of securing or improving FTO does not stop once the results of an investigation are available. Rather, the results of a clearance study provide the tools and intelligence necessary to determine the most desirable course of action for the client (whether a business, a university, or other nonprofit entity) to take in light of the discovery of a so-called *blocking patent*. Counsel should work closely with the decision maker in developing IP risk management strategies. Box 2 presents a representative but by no means exhaustive survey of the principal strategies that may be considered. Any one or a combination of the risk management strategies shown in Box 2 may be employed, as deemed prudent and appropriate by the decision maker working in consultation with counsel. These and other options are further discussed by Krattiger.[9]

8. CASE STUDY: FTO ANALYSIS AND THE LEGAL LIMITATIONS OF A PUBLIC-DOMAIN TECHNOLOGY

The purpose of this case study is to illustrate basic strategies for performing an FTO search of a technology that has both research and commercial objectives. This particular example includes the decision maker's considerations when engaging in an FTO analysis, the process of gathering FTO information in-house, the evaluation by legal counsel, and the outcome of the analysis. Attorney-client confidentiality privileges have been waived for the sake of sharing the experiences of this investigation. The end results of the analysis show that while the target technology, per se, is in the public domain, FTO restrictions are present when it is combined with other technologies.

Legal counsel is often sought when developing commercial products. But the use of FTO searches is not limited to business plans; they may also be crucial to projects with research and social objectives. Platform technologies used in the early phases of product development are of special concern because failing to negotiate access could drastically affect subsequent research and development plans or the licensing value of the technology. Unlike established agricultural biotechnology companies with in-house IP counsel, public sector scientists around the world may not have easy access to legal experts and consequently are often unaware of the IP restrictions on commonly used research tools. Fortunately, to facilitate the research and development of improved crops with commercial and humanitarian objectives, the Public Intellectual Property Resource for Agriculture (PIPRA)[10] is working to design agricultural biotechnologies that are technically strong and subject to minimal IP restrictions.

Plant transformation vectors—the molecular shuttle vehicles that introduce desired genes and traits into bioengineered crops—are a key platform technology in agricultural biotechnology. Plant transformation vectors combine numerous components, such as genetic regulatory elements (promoters), selectable markers, systems to remove those markers, and more. By virtue of the fundamental role that these technologies play in bioengineered crops, they are often protected by intellectual property. Moreover, the FTO pathway quickly becomes entangled and complex because these technologies are usually not used individually but combined with different traits and in numerous host plants. To steer clear of potential blocking patents, it is important to incorporate technologies and methods that are in the public domain (free of IP restrictions) or that can be used with permission. This is why PIPRA, in collaboration with scientific and legal experts, is researching the FTO of various vector components,

Box 2: Options for strategic use of the results of an FTO investigation

Abandon or modify business goal or business practice

If a blocking patent has been discovered and cannot be licensed or avoided, the decision maker must consider whether it is acceptable to abandon pursuit of the affected business goal or the affected business practice (such as the use of a particular research tool or methodology). Alternatively, it may be commercially reasonable to modify the business goal or practice and thus obviate the blocking effect. This process is called "designing around the blocking patent." The effect and cost of the modification must be taken into account to consider the reasonableness of this approach. For example, the decision maker must consider whether FDA approval would be required to change a formulation or manufacturing processes

Take a license, if one is available on commercially reasonable terms

It is important to evaluate the likelihood that the owner of a blocking patent will accommodate the client's business goal by granting an affordable license. Intelligence on this point can be gleaned from reviewing the mission statement of the business or non-profit patentee, as well as from reviewing SEC records or press releases to determine whether the patent in question has been licensed to others. The financial effect the license will have on commercializing the product or technology must also be considered. Royalty payments and manufacturing expenses together account for the cost of goods sold (COGS), so a patent license in effect forces cost cutting in other areas. The pressure on manufacturing costs is even greater for products subject to royalty stacking, when multiple royalties under multiple licenses are needed to commercialize a single product.

Ask the owner of a blocking patent to relinquish their IP rights

Patent owners may consider relinquishing their IP rights in territories or fields of use when they do not foresee sufficiently large commercial markets. In addition, a patentee may find that the benefits of good public relations weigh in favor of relinquishing IP rights for particular humanitarian uses of a technology. In these cases, negotiating a royalty-free license or a covenant not to sue may be possible. However, product liability and stewardship issues remain concerns for many patentees. In fact, potential licensees may find that a patentee is seeking to avoid a liability risk for any defective products incorporating the patented technology that enter the stream of commerce.

Obtain a formal written opinion of counsel

If the consequences of abandoning or modifying the business goal are unacceptable, or if the decision maker suspects or has established that a license may not be available from the patentee on commercially reasonable terms, or if it seems likely that the patentee may take some offensive legal action, counsel may be asked to provide a reasoned written opinion on the non-infringement or invalidity of one or more claims of the blocking patent. It is important for the decision maker to realize that such an opinion does not shield the client against infringement litigation. However, it may provide useful insight or leverage in licensing or settlement negotiations, as well as precluding a court holding of willful infringement (which would permit doubling or trebling of damages).

(Continued on Next Page)

Box 2 (continued)

Leverage the client's own IP portfolio.

Another means of improving the odds of obtaining a license on commercially reasonable terms is to inventory the client's own IP portfolio supporting the business goal (or even other business goals) to determine whether any existing claims (pending or issued) could provide a cross-blocking effect. Can any of the client's claims impede the FTO of the blocking patentee? If none are issued or pending, a client's new patent application may provide a good basis for drafting and prosecuting new claims in pursuit of a cross-blocking effect. Alternatively, if there are issued or pending claims in the client's patent estate that overlap with the patentee's blocking claims, it may be possible for the client to trigger a U.S. patent interference with the patentee. Each of these strategies can provide important leverage in negotiations with the patentee

including promoters used to regulate the expression of desired traits in specific plant tissues.

8.1 *Defining the subject matter of the FTO or clearance search*

The target technology for this case study is a fruit-specific promoter from the tomato E8 gene. Technically, the E8 promoter is often chosen because gene expression under its control is triggered by developmental cues such as fruit ripening. Expression of the gene of interest is confined to the ripe fruit and is not detected in other organs such as leaf, root, or stem. In addition, the promoter can stimulate gene expression in response to a chemical stimulus (ethylene) also in organ-specific fashion. As such, this transcription-regulation element has been used to improve nutritional and juice qualities, extend the vine life of tomato fruit, and express edible human vaccines in tomato fruit.

As previously described, the first step in an FTO investigation is to clearly define the target technology. In this case, PIPRA proposes to use the fruit-specific promoter exactly as described in the initial publications by Deikman and Fischer[11] and Giovannoni et al.[12] The promoters in these publications are virtually identical and consist of about 2,100 nucleotides upstream of the E8 gene. Further promoter characterization disclosing the location and sequence of functional elements within the promoter and upstream nucleotide sequence was reported in Deikman et al.[13] These publications draw the technical boundaries surrounding the target promoter technology and, as we will discuss later, provide important prior art.

8.2 *Does the business plan warrant an FTO analysis?*

The plan of a project sets the direction that an associated FTO investigation will take. In this case, PIPRA foresees that, once this particular promoter is integrated into plant transformation vectors, it will be used for both research and commercial purposes, both within the United States and abroad. Since it will be part of a platform technology that may be broadly adopted, it warrants an in-depth analysis to determine FTO.

Because the technology is being evaluated at an early stage and could be used in a wide range of projects, PIPRA cannot know all of the specific genes of interest that the E8-promoter might be used to drive. Therefore, PIPRA chose to limit the analysis to FTO on the promoter *per se* and not on its use in combination with specific genes of interest, with an understanding that future analyses will be needed to determine FTO for specific combinations of the E8 promoter and heterologous genes. As described before, compounding technologies create a more complex IP landscape because of the potential for overlapping patent claims. This initial FTO analysis thus indicates only the technology's general availability. Still, evaluating limitations at an early stage provides researchers and business developers with

important information about the technology's FTO position and illustrates the legal limitation of a technology presumed to be in the public domain.

8.3 *Case study: FTO information and legal opinion*

In this case, PIPRA provided the background FTO information to legal counsel, who subsequently conducted an FTO analysis. The background FTO information packet consisted of a detailed description of the proposed construct, proposed management strategy of the plant transformation vectors, scientific literature on the technology, and IP search results. Legal counsel assessed the relevant patents, grouping them according to subject matter and assignee, constructed a priority timeline integrating relevant literature and intellectual property (Figure 1), and then delivered an oral and written FTO opinion. The following is a detailed account of the process.

8.3.1 *Client's FTO background information*

The scientific literature in the background file included a list of publications describing the discovery, characterization, and applications of the E8 promoter. Literature records were identified and extracted using keyword and author searches using online databases. Assembling a timeline of publications and contacting the original inventor/author of a technology are advantageous when investigating whether patent protection was sought at the time of invention and publication. This is particularly important because it is possible that corresponding U.S. patent applications could remain unpublished and later emerge as issued patents. PIPRA contacted the principal investigator (PI) of the group that originally identified and characterized the E8 promoter, Robert L. Fischer, at the University of California, Berkeley, and discovered that the inventors did not apply for patent protection prior to their seminal publication. The absence of patent applications by Deikman and Fischer[14] was confirmed by subsequent investigations. Because at this point of the investigation it was presumed that the technology was in the public domain, documenting published literature or *prior art* was particularly crucial.

The patent landscape included patents and patent applications that were closely related to the technology. Keywords and authors of key publications were used to search for patents or patent applications. The patent search engines used were Delphion,[15] M-CAM,[16] and the EPO.[17] A separate search was conducted to identify patents or patent applications that referenced the scientific publications describing the technology. In addition, patented DNA and protein sequence databanks were searched using the E8 promoter's DNA sequence as a query. Because the target technology was identified and characterized in the late 1980s and early 90s, special attention was given to publications with a priority date around that time. After evaluating patents and patent applications, a list was distilled of patents with claims to regions from the tomato-derived E8 promoter. Furthermore, a schematic representation illustrating the claimed DNA sequence between the target technology and patent claims was incorporated (Figure 1). For legal counsel's convenience, a table of patents and patent applications was provided that included record numbers, family members, assignees, publication, priority, and application dates, as well as relevant notes. The patent landscape documentation also indicated whether the patent's nonpatent prior art section (field 56 on the patent coversheet) cited Fischer's publications (evidence that this was considered prior art).

Another independent search was conducted to identify specifically those patents that claim the use of the E8 promoter to drive genes of interest. This search was conducted in the same manner as described above, using keywords for the E8 promoter to search within claims. The pertinent patents and patent applications were extracted and analyzed. Again, a table with the patent records was compiled and a written report with the described information was submitted to legal counsel. After verbal communications and revisions, additional information (such as patent family trees) was provided for analysis (Figure 2).

8.3.2 *Legal counsel's FTO opinion*

Using this background information, legal counsel constructed a priority timeline including the key scientific literature and the most closely related

patent records, which were assigned to Agritope, Epitope, and Monsanto (Figure 1). As shown, the Deikman and Fischer[18] and Giovannoni et al[19] publications initially describe the E8 technology. This precluded the novelty of any subsequent patent claims on the E8 promoter per se (for example, applications filed by Agritope and Epitope). While the detailed written FTO opinion of legal counsel is not included in this report, counsel concluded that the tomato E8 promoter constructs per se (searched as described above, without considering association with any heterologous gene) can be reasonably considered to be in the public domain.

Since the analyses did not examine FTO with the E8 promoter in conjunction with other genes or other vector elements, appropriate FTO limitations and future considerations were highlighted. Interestingly, because the initial E8 publications did not disclose the use of the technology with a variety of heterologous genes, subsequently issued patent claims were able to limit use of the technology by covering novel combinations of already known elements. Thus, while the technology itself is in the public domain, its use with particular genes of interest is not. This information indicates to PIPRA that FTO should be reevaluated in more-advanced stages of the vector construction when other technology components are known. Though not exhaustive, some of the patents claiming chimeric constructs comprising the E8 promoter and heterologous genes are shown in Figure 3. The patents can be grouped into three broad categories related to agronomic characteristics, biopharmaceuticals, and gene expression control. Notice the potential for claim overlap within these broad categories, for instance, gene expression control patent claims may span uses in agriculture and pharma.

Legal counsel conveyed the results of the analysis to PIPRA via oral communications and, subsequently, in a written report. It is important to note that FTO analysis materials are protected by attorney-client privilege and thus should only be shared on a confidential basis with personnel that have a need to know (for example, business decision makers). In the case of the E8 promoter FTO investigation, the client (PIPRA) decided after consulting with legal counsel to disclose the results of the investigation for public informational and educational purposes. ■

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1 See, also in this *Handbook*, chapter 14.2 by Stanley P Kowalski .

2 Ibid.

3 See, also in this *Handbook*, chapter 14.1 by Anatole Krattiger.

4 See, also in this *Handbook*, chapter 7.3 by Alan Bennett.

5 The scope of this exception has been the subject of analysis. An informative publication on the definition of "essentially derived" can be found at www.amseed.com/pdfs/EDVInfoToBreeders_0605.pdf.

6 The *Madey v. Duke Univ*. case was based on a dispute between employer and employee, rather than a commercial firm's decision to sue a university.

7 www.sec.gov.

8 www.sec.gov/edgar.shtml.

9 See *supra* note 3.

10 www.pipra.org.

11 Deikman J and RL Fischer. 1988. Interaction of a DNA Binding Factor with the 5'-Flanking Region of an Ethylene-Responsive Fruit Ripening Gene from Tomato. *Embo J*. 7(11):3315-20.

12 Giovannoni JJ, D DellaPenna, AB Bennett and RL Fischer. 1989. Expression of a Chimeric Polygalacturonase Gene in Transgenic Rin (ripening inhibitor) Tomato Fruit Results in Polyuronide Degradation but not Fruit Softening. *Plant Cell* 1(1):53-63.

13 Deikman J, R Kline and RL Fischer. 1992. Organization of Ripening and Ethylene Regulatory Regions in a Fruit-Specific Promoter from Tomato (Lycopersicon esculentum). *Plant Physiol*. 100:2013-17.

14 See *supra* note 11.

15 www.delphion.com.

16 www.m-cam.com.

17 www.european-patent-office.org.

18 See *supra* note 11.

19 See *supra* note 12.