Freedom to Operate: The Preparations

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ABSTRACT

Freedom to Operate (FTO) is the ability to proceed with the research, development and/or commercial production of a new product or process with a minimal risk of infringing the unlicensed intellectual property (IP) rights or tangible property (TP) rights of third parties. The procedure for assessing whether the product or process possesses FTO is called the FTO analysis, performed by meticulously dissecting the product or process into its fundamental components and then scrutinizing each for any attached IP or TP rights. The early preparations for an FTO analysis are crucial, because they will influence all that follows and hence determine the quality of the work product. Thorough preparation will lay a solid foundation, supporting a credible and reliable FTO analysis. This chapter explains these preparations through an example.

1. INTRODUCTION

1.1 *Freedom to operate defined*

Access to agricultural biotechnology (agri-biotech) and pharmaceutical (pharma) products, including vaccines, and processes can help developing countries improve public health and nutrition, contributing to the well-being of those most in need. Such products and processes are categorically technically complex. A cursory glance at a "materials and methods" section of any paper published in a scientific or medical journal reveals the plethora of components and processes that are routinely employed in the research, development, and eventual commercialization of an agri-biotech or pharma product. This technical complexity mirrors the corresponding intellectual property (IP) rights and tangible property (TP) rights complexity; that is, each component, process and/or combination thereof that went into the product might have either IP rights (for example, patents) or TP rights (for example material transfer agreements [MTAs]) of other parties attached. Hence, an agri-biotech or pharma product/process might not be "clean" in a legal sense, meaning that moving ahead with research, development, and commercialization could constitute infringement of another's IP or TP rights. However, the risk of infringement liability can be systematically managed and dramatically reduced. This is what freedom to operate (FTO) is all about.

Broadly defined, FTO means the ability to proceed with the research, development and/or commercial production, marketing or use of a new product or process with a minimal risk of infringing the unlicensed IP rights or TP rights of third parties.[1] The procedure for assessing whether or not the product or process possesses FTO is called the FTO analysis. An FTO analysis is performed by meticulously dissecting the product or process into its fundamental components and then scrutinizing each for any attached IP or TP rights. It is critical to make clear, however, that an FTO

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analysis neither explicitly nor implicitly denotes an absolute *freedom* to operate, but is instead a risk management tool, the purpose of which is to assess the *likelihood* for infringement-litigation liability associated with the new product or process: an FTO is therefore an informed, reasoned, and calculated *best estimate* of infringement liability, in a given jurisdiction, at a given period of time (that is, a snapshot assessment of the contours, canyons and crevasses of the IP/TP rights landscape for the specific product or process).[2]

Thus, an FTO analysis will inform an institution or company that the research, development, and commercialization of the new product or process may proceed with a minimal risk of infringing the unlicensed IP rights and/or TP rights of others.[3] However, as the IP/TP rights and legal landscape changes, shifts, and evolves, the dynamics and results of the FTO analysis may also change. (For example, patents may issue, expire, or be invalidated; licenses may be granted or terminated; patents may be assigned and then reassigned.) Also, patent rights are strictly territorial,[4] meaning that a product/invention might possess FTO in one jurisdiction (a nation where a relevant patent has not issued) but, on the other hand, would not possess FTO in another jurisdiction (a nation where a patent has issued). Therefore, the results of an FTO analysis must be periodically reassessed and updated where and when appropriate.[5]

1.2 *FTO analysis preparations: overview*

The FTO analysis must be organized, logical, methodical, meticulous, and carefully documented. An important initial step in a thorough FTO analysis (that patent counsel may then subsequently use to draft an FTO opinion) is the completion of the following preparations:

- assembling the FTO team
- analyzing, understanding, and dissecting the technology
- assessing plant pedigrees
- recognizing pharmaceutical technical considerations
- interviewing the researchers
- locating notebooks, lab records, and computer files
- finding MTAs, bag-tags, bags of seed, and any unknown property trail
- formulating the series of FTO questions
- selecting scientific databases
- selecting patent databases
- identifying special resources for pharmaceutical patent information
- understanding U.S. Patent and Trademark Office (PTO) information (file wrappers and disclosures)
- remaining aware of the 18-month "period of silence"
- maintaining due diligence throughout the FTO analysis

In this chapter, each of the aforementioned preparative steps is explained within the context of preparing for and conducting a successful FTO analysis. Applicable technologies might be either agri-biotech or pharma. Although the materials, methods, and tools used may be dissimilar from agri-biotech to pharma, the fundamental FTO principles and procedures remain unwavering for each of these. Hence, by following this FTO analysis blueprint, a series of sound FTO questions can be formulated, so as to lay a solid foundation from which a reliable FTO analysis will be able to develop. Patent counsel can then draw upon this analysis to formulate either one or a series of FTO opinions.

1.3 *Illustrative example*

Throughout this chapter, in order to help clarify and exemplify the topics covered, an illustrative hypothetical will be employed. It is a *purely fictionalized* situation, presented solely for the purpose of focusing the discussion and facilitating understanding.

1.3.1 *Background*

Recently a new viral disease has emerged in east Africa. The causative agent is a virus, simian in origin, having been asymptomatically endemic in an isolated population of pygmy desert baboons for millennia. The scourges of war, famine, and drought have impelled many people to seek sustenance from bush meat, which they eventually find by scouring the wilderness for days on end.

It is believed that the pathogenic virus made the leap from baboon to human when famished refugees consumed uncooked baboon meat infected with the virus, which likely rapidly entered the bloodstream via the portals of ulcerated oral lesions caused by advanced scurvy. Upon entering the new host, the virus migrated to skeletal muscles, where, in contrast to the primary baboon host, the virus causes progressive muscular degeneration with symptoms resembling myasthenia gravis. It is colloquially referred to as the "fall-down disease" (FDD). The most serious concern with this emergent disease is that it appears to be readily transmissible from human to human via bodily secretions. Hence, it may have the capacity to spread throughout crowded refugee facilities, creating even more suffering and death.

The sudden appearance of this deadly virus has prompted a series of research and development efforts across the globe. These include developing techniques to raise the virus (it can only be cultured in monkey cells), sequencing and characterizing the viral genome, cloning the battery of genes that encode the viral proteins, and developing candidate vaccines.

An east African nation is home to the Institute of Dry Land Crop Research (IDLCR). This nation has recently acceded to the World Trade Organization (WTO) and is serious about becoming compliant with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) so that it can increase economic growth, for example by attracting greater foreign direct investment, particularly in the areas of emerging technologies, such as, biotechnology. As a result, a greater number of foreign interests are filing patent applications for their biotechnological applications and technologies in this nation, usually as part of the national-phase filing pursuant to the Patent Cooperation Treaty (PCT).

In response to the looming crisis of the emergent viral disease FDD, the IDLCR, in conjunction with this nation's leading medical research center, has launched a program to produce a large quantity of viral antigen in recombinant grain sorghum, transformed with the most immunogenic of the viral antigens. This will then be used to produce large amounts of vaccine to immunize thousands of displaced refugees. Such a research and development program will inevitably entail numerous proprietary components and techniques, likely having the IP and TP rights of third parties attached. Therefore, FTO issues will be a very real and constant concern.

2. ASSEMBLING THE FTO TEAM

2.1 *Skilled leadership of the FTO team*

From the very start of an FTO analysis, it is absolutely essential to establish credible, capable, competent leadership so that the FTO analysis is properly conceived, organized, and conducted. Because an FTO analysis is a multidisciplinary endeavor, the team leader must ensure that it remains focused, on-course, and precise. Under ideal circumstances, that is, qualified patent counsel is available and affordable, such counsel should lead the way. However, in many situations this might not be possible. Also, depending on the stage of the FTO analysis, patent counsel leadership might not be required. For example, early stages of a preliminary FTO analysis can be performed in lieu of counsel, possibly in order to assess or survey the IP rights landscape. Counsel may be sought later when and if it is warranted, possibly at later stages of the FTO analysis when questions of legal significance arise (for example, patent claims analysis). At such a stage, one possible route would be to seek pro bono counsel via services provided by public interest associations (for example, Public Interest Intellectual Property Advisors [PIIPA]).

In order to be most effective, the FTO team leader ideally should have expertise in agri-biotech and/or pharma, depending on the exact product and/or process undergoing FTO analysis. Furthermore (if patent counsel will not initially lead the FTO team) the FTO team leader must be the available professional with the greatest expertise in IP-related issues (for example, a technology-transfer professional officer, an intellectual property practitioner such as a patent agent or a scientist who has participated in various IP rights and technology-transfer courses, workshops, and/or seminars). The FTO

team leader must understand the dynamics of the step-by-step process of FTO analysis, not only within the legal paradigm, but also from a sophisticated technical and scientific perspective. Because an FTO analysis is conducted at the interface of science and law, the FTO team leader must be professionally amphibious (that is, capable and comfortable in two different professional environments).[6]

2.2 *The FTO team is multidisciplinary*

The FTO team leader selects who will be part of the FTO team. FTO team members should include: scientists who had supervised the project, technology transfer personnel, and technicians/support staff. The last are absolutely essential, as they frequently know what *really* happened during product research, development, and commercialization. The FTO team might also include business personnel (depending on the stage of commercialization) and possibly administrative staff. The latter might have information pertaining to relevant communications, documents, and agreements. It is also very important to note that the FTO team may, or may not, be the same as the client. For example, the actual client might be a research institute, and the FTO team would be composed of employees.

2.3 *Work product doctrine and patent counsel*

One important reason that it is judicious to have patent counsel lead the FTO team, particularly at later steps in the analysis, pertains to maintaining the confidentiality of documentation. In the event that a claim of patent infringement arises, the FTO analyses and opinions, prepared under the guidance of patent counsel, may be protected from discovery (the compulsory disclosure of documents to an opposing party), pursuant to the attorney work-product immunity doctrine. However, it is unclear how far this immunity reaches, and so one must exercise caution. In general (in the United States), "*[pursuant to the U.S. Federal Rules of Civil Procedure, Rule 26(B)(3)] written material and mental impressions prepared or formed by an attorney in the course of performing legal duties on behalf of a client are protected from discovery as the attorney's 'work product' in the absence of undue prejudice or hardship to the party seeking discovery.*" In spite of this, "*there has been disagreement among courts construing this language as to its proper interpretation and its integration with other doctrines impacting on discovery jurisprudence … With respect to the standard of protection from discovery which an attorney's opinion work product should be given, a few courts have held that Rule 26(b)(3) mandates absolute protection, while a growing number of the more recent decisions have held that the standard of protection is less than absolute, with the strict protection generally afforded an attorney's opinion work product allowing for exceptions in certain circumstances.*"[7] Such complex issues relating to work-product immunity, and the extent to which it might reach, further illustrate the advisability of having qualified patent counsel as the FTO team leader.

After the FTO team is assembled, the leader coordinates, leads, and guides the team throughout the entire FTO analysis.

2.4 *The importance of scientific understanding*

In the case of FDD vaccine development, the IDLCR FTO team leader must carefully select a cadre of scientists who will, collectively, comprehend the spectrum of biological, genetic, agronomic, and biotechnological components and techniques that will go into the research, development, and commercialization of the vaccine. These individuals will form the basis of the FTO team. In addition, other professionals might be selected, such as technology transfer officers, administrators, and business managers. This team will then be poised to begin the arduous task of FTO analysis.

3. ANALYZING, UNDERSTANDING AND DISSECTING THE TECHNOLOGY

3.1 *Product deconstruction*

As the initial step in the FTO analysis, the FTO team must thoroughly know the precise nature of the technology itself, whether it is a product, process, or combination thereof (referred to hereinafter as the product/invention). In order

to accomplish this, the FTO team must work closely with all of the research and development staff, so as to understand the nature of the technology to such an extent that it can be "disassembled" into its fundamental components, that is, *deconstructed.*[8]

Therefore, in the deconstruction phase of the early preparations for the FTO analysis, the FTO team and any other scientists, collaborators, or staff, work together to resolve the product/invention into the fundamental processes used to make it, the components that went into its construction, and any possible combinations of processes and/or components potentially pertinent.

3.2 *Research tools*

At this stage it is important to identify any research tools that were used during research and development of the product/invention.[9,10,11] Research tools, integral for the efficient development of commercial applications both in agri-biotech and pharma, are defined by the National Institutes of Health (NIH) as the "*full range of resources that scientists use in the laboratory including [a fragment of a gene, a gene], cell lines, monoclonal antibodies, reagents, animal models, growth factors, combinatorial chemistry and DNA libraries, clones and cloning tools (such as PCR), methods, laboratory equipment and machines, databases and computer software*."[12,13] Identifying them is a critical step in the early FTO analysis preparations, because, although seemingly ubiquitous and readily, even "freely," available in many laboratories, there nevertheless appears to be no research tool usage (experimental use) exemption in the United States. To assume otherwise would be to unwisely overlook and thereby disregard important steps in the product/invention undergoing FTO analysis.[14]

3.3 *Components of the vaccine*

In the case of FDD vaccine development, the production and deployment of a vaccine from transgenic sorghum would entail numerous components and technologies, including, but not limited to:

- monkey cell culture (for viral propagation)
- antibodies against the viral proteins
- the viral genome
- individual viral genes
- research tools used to clone the viral genes (for example, the polymerase chain reaction [PCR], and related techniques)
- plant transformation techniques (for example, *agrobacterium* and/or bio-projectile methodologies)
- plant genetic transformation constructs (for example, vectors, promoters, transit peptide sequences)
- plant cell culture techniques and cell lines
- sorghum germplasm used for genetic transformation
- procedures for harvesting and purifying expressed antigen
- formulation, production and delivery of the actual vaccine

Each of the above would most likely represent a deconstructed piece of the contemplated final vaccine, and each would therefore constitute an FTO question (see section 8) that the FTO team would subject to thorough scrutiny in the FTO analysis.

4. IP AND TP RIGHTS

At this stage, it will be instructive to briefly and clearly define some of the forms of IP and TP rights that are commonly encountered in an FTO analysis.

4.1 *Patents*

Patents, as referred to in this paper, are utility patents: a grant by a government to an inventor, for the right to exclude others from making, using, or selling his or her invention, for a specified term of years. This is done in exchange for the inventor fully disclosing the invention in the patent document (typically the specification). Hence, a patent can be viewed as a contract between the inventor and the government, wherein the inventor provides full disclosure of the invention in exchange for absolute exclusivity to the IP rights for a specified term. Patents are applicable to both agri-biotech and pharma.[15]

4.2 *MTAs*

MTAs are legal instruments that typically accompany the transfer of TP. They usually (possibly *ideally*) document *what* is transferred, *who* transfers to *whom*, as well as the provisions, uses, scope of rights, confidentiality, and term of the agreement.[16] MTAs are legally defined as bailments.[17] So, the question naturally arises, what is a bailment? A bailment is the delivery of an item of TP from one party to another, for a specific purpose, pursuant to the terms of a contract. However, in a bailment it is critical to remember that although there is a change in the actual physical *possession* of the property, there is no transfer of *ownership*: title remains with the owner (bailer)—even though possession has shifted to the recipient (bailee).[18] In addition to being a bailment, an MTA also entails contractual obligations, and hence, as a binding contract, the terms and provisions of an MTA must be taken very seriously by both parties involved in the transfer/transaction, so as to avoid the possibility of breach of contract liability.[19]

The terms and provisions of MTAs can vary considerably, particularly when comparing MTAs executed by the nonprofit sector (for example, universities) with those executed by the for-profit sector (for example, corporations).[20] Confidentiality, publication rights, and reach-through rights may vary significantly, and one must exercise caution so as not to agree to an MTA with potentially onerous terms.[21] If the material used in the development of the product or process was obtained in violation of an MTA between two other parties, then the "obtainer" of the material may be liable for unauthorized use. For example, Andy transfers (technically speaking bails) a plasmid to Roberta (with specified contractual obligations attached), which is then "obtained" by Carl, via trick, theft, or other nefarious means, and Carl then uses it to either develop, or incorporate into, his product/invention. Carl might very likely have a liability problem—possibly misappropriation of Andy's tangible property.[22] MTAs are applicable to both agri-biotech and pharma.

4.3 *Bag-tags*

Bag-tags, a type of agri-biotech TP rights protection, are enforceable contracts[23] that restrict the licensee (grower) in the use and/or reuse of seed.[24] The bag-tag license is analogous to shrink-wrap, box-top, and tear-me-open software license transactions, such that an implicit contract is formed when the seal is broken, which then obligates the grower to the terms of the license as articulated on said seal.[25, 26]

4.4 *Plant/germplasm protection*

4.4.1 *Plant IP rights statutes*

Germplasm IP rights protection (agri-biotech) exists in various forms, with each form addressing different types and levels of what is protected. In the United States, the Plant Patent Act (PPA), the Plant Variety Protection Act (PVPA), and Utility Patents for Plants (UPP) are the statutory forms of germplasm IP rights available.[27] The PPA provides IP rights protection for asexually (vegetative) propagated plants, (for example, plants that are propagated from cuttings or by budding or grafting); tuber-propagated plants (potato varieties) are not covered by the PPA. The PVPA provides IP rights protection for sexually propagated plant varieties, F_1 hybrids, and also tuber-propagated plants (potato varieties); plant varieties must meet the new, distinct, uniform, and genetic-stability requirements. With UPP, the level of IP rights protection is much broader than that afforded by either the PPA or the PVPA. The PPA and PVPA only confer IP rights protection for certain plant varieties, but UPP can claim plants, plant varieties, plant parts, seeds, and tissue cultures.[28, 29]

4.4.2 *Plant IP rights treaties*

In addition to the PPA, PVPA, and UPP, there are two treaties that address germplasm IP rights protection: the International Treaty on Plant Genetic Resources for Food and Agriculture (PGRFA)[30] and the Convention of the International Union for the Protection of New Plant Varieties (UPOV).[31] In PGRFA, important provisions include an agreement not to claim IP rights for any of the germplasm resources "*in the form received*" from the multilateral system. There is also a benefit-sharing scheme triggered by the commercialization of new plant varieties.[32, 33] A treaty seeking to impart international conformity in

plant variety protection, UPOV, fundamentally consistent with the PVPA, specifies that the fundamental criteria for IP rights protection are distinctiveness, uniformity and stability.[34]

4.5 *Technology-use licenses*

Technology-use licenses may need to be sought for the use of certain research tools (see section 6.2), which frequently are indispensable in order to facilitate the research and development phase of an agri-biotech or pharma product, process, or application.[35] Although there is currently considerable debate as to whether the patenting and licensing of research tools should be subject to either experimental use exceptions or compulsory licensing schemes,[36] the basic presumption should remain that there is no experimental use exemption for research tools, regardless of whether the work is performed in a profit or nonprofit entity.[37]

5. ASSESSING PLANT PEDIGREES

5.1 *The complexity of plant-related IP rights*

When analyzing an agri-biotech product/invention, it is necessary to determine the pedigree of the germplasm forming its very foundation. In other words, the trail of germplasm, with as much detail as possible, must be traced and documented. If detailed breeding records are available, this task will be much easier. Hence, the FTO team must ask these questions: What type of germplasm is the product/invention embedded in? Where did this germplasm come from? What is the detailed pedigree of the germplasm?

Furthermore, as already discussed hereinabove, plant germplasm may be protected by various overlapping forms of IP rights:

- trade secrets (primarily for proprietary inbred lines, for example, in hybrid maize breeding)[38]
- utility patents[39]
- Plant Variety Protection Act (PVPA)[40]
- Plant Patent Act (PPA)[41]
- UPOV (as consistent with the PVPA)[42]
- PGRFA (for germplasm accessed from the multilateral system)[43]

Hence, the FTO team must remain aware of the possibility of a complex IP/TP rights situation with regard to germplasm. It must therefore proactively corral as much information as possible.

5.2 *Germplasm issues*

Concerning *in planta* expression of viral antigen in transformed sorghum, varieties contemplated for genetic transformation with the viral gene(s) will likely present complex germplasm considerations during the FTO analysis. For example, overlapping forms of IP and TP rights protection might apply: an ideal sorghum line could simultaneously have third-party patent and plant variety protection rights attached. Since the nation where the IDLCR is located is seeking to comply with the TRIPS Agreement, it will likely have a UPOV-harmonized PVPA enacted as statutory law, and certainly also a patent statute. Hence, germplasm issues, occasionally (and foolishly) subordinated to patents in an FTO analysis, will be of critical importance.

6. RECOGNIZING PHARMACEUTICAL TECHNICAL CONSIDERATIONS

6.1 *Pharma components*

As with agri-biotech, when examining a pharma product/invention the FTO team will need to consider pharma-product/process-specific components.[44]

The compound itself must be considered:

- crystalline form
- amorphous form
- enantiomers
- metabolites
- prodrugs

The types of pharmaceutical compositions must also be considered:

- delivery systems
- vehicles
- adjuvants

The methods, steps, and components involved in the product synthesis are also critical (see also section 6.2):

- steps and the reagents and techniques that compose each step
- intermediates (For example, for a five-step synthesis, there are at least four intermediates to clear and four sets of the reagents that are used to convert the intermediates.)[45]
- reagents (For example, "*Before launching an all-out patent search, it is often productive to search your old organic chemistry/biochemistry textbooks and Aldrich/Sigma catalogs, and ask two questions: (a) what chemical utilities and processes are clearly within the public domain, or (b) can be purchased from vendors that can sell them to you for unrestricted use?*")[46]
- purification techniques and protocols
- handling techniques and procedures

Methods of use, that is, downstream considerations, also are important to keep in mind:

- modes of treatment
- dosimetry
- limiting side effects

6.2 *Research tools*

And finally, but no less important, research tools must be considered. Biotechnology research tools are used in the development of drug products, therapeutic devices, or diagnostic methods. These research tools are not themselves physically incorporated into the final product/device/diagnostic. Hence, they represent the full range of resources used in drug discovery and development.[47] (See also section 3.2.)

6.3 *Vaccines*

In the case of vaccines, there are additional FTO analytical considerations specific for vaccine research, development, manufacture and deployment, including:

- expression systems
- fusion partners
- immunostimulators
- adjuvant systems
- excipients
- delivery devices[48]

As with the pharma product/invention, the FTO team must carefully analyze each of these and, using the results of this analysis, formulate an appropriate series of FTO questions (see section 8). In the case of the FDD vaccine FTO analysis, there will be:

- upstream considerations (for example, the viral genes, monkey cell culture, cloning)
- midstream considerations (for example, sorghum germplasm and plant transformation, *in planta* antigen expression)
- downstream considerations (for example, vaccine formulation, production, optimization [adjuvant selection] and delivery)

As already discussed, each of these will likely have third-party IP and/or TP rights appurtenant.

7. INTERVIEWING RESEARCHERS AND LOOKING FOR RECORDS

7.1 *Interviews and laboratory history*

To ensure success when performing the FTO analysis, a continuing rapport between the FTO team and scientific and technical staff is essential. This will help keep everyone involved on the same track, maintain momentum, and keep the FTO analysis up and running. Such informal dialogues with research personnel can reveal critical snippets of information, such as the trail of acquisitions. (For example, who got what from whom, and was it with or without proper authorization as to embedded IP and/or TP rights?) Consider this hypothetical scenario: Andy obtains a product component from Roberta, who had previously obtained it from Carl. However, there was no proper authorization (for example, no MTA) for such a transfer in the first instance, which is definitely something that the FTO team needs to know.

Such anecdotal narratives can never be found in a paper trail; these are solely preserved in the "oral history" of the laboratory. Thus, the FTO team must, at times, function as investigative cultural anthropologists, sorting through the history, habits (possibly bad habits), and "traditions" of a laboratory and research group. Additionally, this sort of dialogue will also help researchers to recall more fully what they had done, allowing them to

fill gaps in the written records. What is in the laboratory notebooks may only be part of the story.

7.2 *The paper trail*

Still, the FTO team must tenaciously pursue every paper trail, searching the laboratory offices, greenhouse, and even the field house, in order to track down notebooks, laboratory records, associated paperwork, computer files, MTAs, bag-tags, bags of seed, and any evidence suggesting an unknown tangible property trail, misappropriated property, or unauthorized access to a third party's confidential information. A comprehensive review of the research and development group's written and oral records and related information will thereby enable the FTO team to acquire a sophisticated understanding of what the product/invention is and what IP and TP rights might be involved.

After the FTO team has identified and understood each of the fundamental units of the deconstructed product and/or process, they then can use this information to frame a series of "FTO questions."

7.3 *Template for FTO questions*

For the FDD vaccine, the product deconstruction table (Table 1) concisely summarizes the components and process that go into its research, development, and commercialization, as well as the potentially appurtenant third-party IP and TP rights. This is the template, the roadmap, from which the FTO questions (see section 8) can be formulated, addressed and analyzed.

8. FORMULATING THE FTO QUESTIONS

Following the technical deconstruction of the product/invention, a series of FTO questions are formulated.[49] These questions are structured to systematically analyze the dissected processes, components, and any combinations thereof, for potentially embedded IP rights (for example, patents and trade secrets) and TP rights (for example, MTAs and bag-tags[50, 51]). Each FTO question, therefore, asks whether a method to make, a material used to make, or any combination of methods and materials, has, or may have, third-party IP or TP rights attached. Thus, a *single* material or method, used in the development of either an agri-biotech or pharma product/invention, may have multiple proprietary issues, that is, both an IP right (for example, a patent right) and a TP right (for example, an MTA) of potential relevance. The gravity of formulating a correct series of FTO questions, then, underscores the necessity for caution and meticulousness at this early stage in the FTO analysis, because all the work that follows is built upon this foundation.

9. SCIENTIFIC DATABASES

Note: scientific database searches and patent database searches are mutually reinforcing, that is, the two support, verify, guide, and inform each other throughout the process of the FTO analysis. For example, inventors might be authors; institutions might be assignees; scientific discoveries might be the actual invention (disclosed in a scientific publication).

Scientific database searching, along with patent database searching, are integral to the FTO analysis. This is where the FTO team assembles the piles of raw information and data, both written and anecdotal, that will subsequently be parsed, analyzed, and organized in order to address the FTO questions that the FTO team has formulated. Furthermore, the FTO team needs to know what types of scientific informational resources are available, both freely and also on a premium, value-added, pay-per-view basis. Furthermore, the FTO team needs to understand what constitutes the value added for the pay-per-view databases, so that they will be used according to specific needs at certain times in the FTO analyses in the most cost-effective manner.

There are many examples of scientific databases. For example, freely available ones include:

- Agricola[52]
- Google™[53]

Whereas premium value-added, pay-per-view databases include:

- Biosis[54]
- Current Contents[55]
- Cab Abstracts[56]

Table 1: Product Deconstruction, FDD Transgenic Vaccine

Technological component, process, or tool	Proprietary protection, likely appurtenant	Relevant documents
Monkey cell culture (for viral propagation)	IP Rights, TP Rights	patents, MTAs
Antibodies against the viral proteins	IP Rights, TP Rights	patents, MTAs
The viral genome	IP Rights	patents
Individual viral genes	IP Rights	patents
Research tools used to clone the viral genes (for example, the polymerase chain reaction [PCR], and related techniques)	IP Rights	patents, technology-use licenses
Plant transformation techniques (for example, *agrobacterium* and/or bio-projectile methodologies)	IP Rights	patents, technology-use licenses
Plant genetic transformation constructs (for example, vectors, promoters, transit peptide sequences)	IP Rights, TP Rights	patents, MTAs
Plant cell culture techniques and cell lines	IP Rights, TP Rights	patents, MTAs
Sorghum germplasm used for genetic transformation	IP Rights, TP Rights, possibly trade secrets (for example, if variety was developed using parental lines protected as trade secrets)	patents, plant variety certificates, possibly MTAs (for example, if germplasm is covered by the PGRFA), bag-tag licenses
Procedures for harvesting and purifying *in planta* expressed antigen	IP Rights	patents
Formulation, production, and delivery of the actual vaccine	IP Rights, TP Rights, trade secrets (for example, confidential third-party know-how and/or show-how protected as trade secrets)	patents, MTAs, technology-use licenses

10. PATENT DATABASES

10.1 *Free and premium databases*

As with scientific databases, the FTO team needs to know what resources are available vis-à-vis patent databases, both freely available and premium value-added, pay-per-view. The FTO team should also know the type of value added for the pay-per-view databases. These databases can then be accessed according to specific needs at key stages in the FTO analyses.[57]

For example, freely available patent databases include:

- PTO[58]
- esp@cenet®[59]

And premium pay-per-view (with value-added features) patent databases include:

- Delphion[60]

10.2 *Pay-for-view, value-added features*

For purposes of illustration, some of the value-added features of Delphion that distinguish it from either the PTO or esp@cenet are discussed here. While free patent research sites can provide patent records, they do not offer the analytical and productivity tools needed to make sense of the data in those records. What follows are some of the key features of Delphion that can make this fee-based service the right choice at the right time in the FTO analysis.[61]

Rather than presenting just a patent record, the primary display record on Delphion is an integrated view that provides a cross-collection of information without the need to perform extra queries. Included in the integrated view are:

- family information showing the countries in which an invention is protected
- the Derwent World Patents Index (DWPI) title and abstract written in English using clear, concise, industry-specific terms
- accessible references to both patent and nonpatent prior art
- extensive hyperlinking to a variety of related information—including definitions for the fields contained in the integrated view

Delphion offers pay-per-use searching of the value-added DWPI database, which covers 13 million unique inventions and has a unique hierarchical system of coding allowing extra precision and accuracy in searching. DWPI data can be used in most of the Delphion analytical and productivity tools. The Delphion Snapshot analytical tool creates quick, easy-to-read bar charts allowing summarization of key bibliographic data—and then further refinement of those summaries. Delphion Work Files allow the saving of result sets or groups of patents that are to be reviewed for future reference. One can easily share these Work Files with colleagues, thus allowing worldwide collaboration. And one can also use analytical tools, like Snapshot, to perform further analyses of these groups of hand-selected records. Delphion allows a user to save frequently used queries, thus eliminating the need to reconstruct them each time. This saves time and decreases the chance for errors to occur in queries. Saved searches can be set to run automatically, advising one of the search results. Data Extract exports more than 50 key bibliographic fields in formats designed for use in other popular applications. The Family Legal Status reports the current legal status of the family members of the invention being examined, which means that there is no need to individually search for each member of the family in order to ascertain the overall view of the protection in each jurisdiction. Delphion, as part of the Thomson Scientific family of IP solutions, offers all the advantages of working with a worldwide company, including a robust infrastructure and support network, interoperability with other Thomson Scientific solutions, and a global perspective on IP research and management.

11. PHARMACEUTICAL PATENT INFORMATION

A pharma product/invention, has, in addition to the standard patent search tools and resources listed hereinabove, its own patent resource materials. These include the Orange Book, the Merck Index, and the actual physical "shoes" at the PTO.

11.1 *The Orange Book*

The Orange Book, "*is an FDA-published document available in paper and electronic form that lists all FDA-approved drugs with any patents pertaining thereto.*"[62] The Orange Book contains approved drug products with therapeutic equivalence,[63, 64] as well as the expiration dates of patents on therapeutic small molecules and on approved indications and compositions.[65] The Orange Book is available as a printed, bound edition, complete with an orange cover, or online.[66]

11.2 *The Merck Index*

The Merck Index lists patents and publications on older drugs and reagents.[67] It is available as a printed edition or online.[68]

11.3 *PTO shoes*

When working with a pharma product/invention, a hand search of the "shoes" in the PTO may be prudent.[69] This is an actual physical paper search, within the shoes: the boxes containing patent prior art.[70] This is sometimes necessary due to the differences in nomenclature used by various patent drafters, differences that might not be readily identified and sorted out in electronic searching. Hence, under certain circumstances, the physical shoe search is an added measure of due diligence.

12. PTO INFORMATION

In addition to searching scientific and patent databases, and checking the Orange Book, Merck Index, and the PTO shoes, there are several other resources of which the FTO team needs be aware. These include patent applications and the patent file wrapper.

12.1 *The patent file wrapper*

A very specialized informational resource is the patent file wrapper. The file wrapper is a physical folder, held by the PTO. It contains documents pursuant to the patent application and prosecution, including the original patent (or trademark) applications, as well as any amendments, affidavits, and written arguments submitted by the applicant, and the actions taken by the examiner concerning the application.[71] The file wrapper becomes publicly available only after the patent issues. The file wrapper can be either physically accessed,[72] or accessed via a searchable, writable, PDF format, which requires an up-to-date version of Adobe® Reader® and sufficient RAM (random-access memory) on the searcher's computer.[73]

12.2 *Patent counsel analyzes the patent file wrapper*

Since the file wrapper is such a specialized informational resource, it will typically be accessed and analyzed during an FTO analysis specifically to address very technical issues (for example, claims interpretational queries, usually done only near the terminal phase of the FTO analysis). Furthermore, the file wrapper should be searched and analyzed only by qualified patent counsel, who ideally, at this late stage in the FTO analysis, is the leader of the FTO team. This is because counsel, by reviewing any patent claim amendments or disclaimers, will be using the contents of the file wrapper to carefully construe the precise meaning and scope of the claim language.[74, 75] It is important to recall that an FTO analysis proceeds from broad and general to narrow and precise. Correspondingly, the analysis of patents proceeds from the patent itself (the abstract, claims and specification) to the claim language construction, to the file wrapper contents.[76] Hence, the greater the precision and specificity of the analysis, the greater the advisability for patent counsel participation: the ability to understand the legal basis of claim meaning and scope become critical at the later stages of the FTO analysis.

12.3 *Patent applications*

Patent Applications are filed with the PTO, the PCT, and also in the various National Phase Applications. Although patent applications do not technically confer statutory IP protection, they nevertheless are a good indicator of what might be subject to protection pending patent issuance.

13. THE "PERIOD OF SILENCE"

It is critical to understand that patent applications will not be available prior to publication, and so

their contents remain unknown for a period of 18 months after the earliest effective filing date.[77] Therefore, whereas such inventions are held in trade-secret status during this period, they nevertheless are still pending as *potential future patents*. However, under U.S. law, if the patent application is only to be filed in the United States, then the 18-month rule may not apply. (That is, the applicant may opt out of the 18-month requirement, and in that case the invention, as disclosed in the patent application, remains a trade secret until patent issuance.[78]) The 18-month period of silence, therefore, has implications in the FTO analysis, in that there may be pending IP rights, still below the surface, but nonetheless relevant to the FTO analysis. A diligent analysis of the published scientific literature, including conference papers, abstracts, and presentations, might suggest what pertinent IP rights are lurking in patent applications still hidden during the 18-month period.

14. DUE DILIGENCE

During the preparation, set-up, data accumulation, and FTO question-formulation stages of an FTO analysis, due diligence is required. *Due diligence*, broadly defined, is "*Such a measure of prudence, activity, or assiduity, as is properly to be expected from, and ordinarily exercised by, a reasonable and prudent [person] under the particular circumstances; [Due diligence is] not measured by any absolute standard, but [depends] on the relative facts of the special case.*"[79] From a practical standpoint, due diligence necessitates a methodical approach, such that all forms of IP and TP rights are garnered, organized, and assembled into a coherent document, for example, a Microsoft Excel spreadsheet.[80] The question often arises, as to how much diligence is enough. The answer? When one finds oneself treading the same ground, then the requirements of due diligence are satisfied.

15. CONCLUSIONS

The preparations for an FTO analysis will determine the quality of the final work product. Organization, thoroughness, meticulous documentation, and solid leadership by a capable FTO team leader will all combine to contribute to a successful outcome. A comprehensive checklist of what must be established during the early stages of the FTO analysis serves as a helpful tool.[81] For example, the list should include:

- possible pertinent patents, including their prosecution and/or litigation status
- patent applications
- third-party trade secrets, including whether they might have been misappropriated
- all third-party TP rights
- all research tools used to make the agri-biotech product or pharmaceutical innovation
- any agreements (for example, trade secret licenses, MTAs, bag-tag [shrink-wrap], or technology-use licenses, noting conditions and restrictions appurtenant)

And finally, it is imperative that all records are properly maintained. Consistent records of all searches and search terms must be documented and organized. This should include:

- spreadsheets of all FTO search results
- records of search terms used
- databases searched
- interviews with researchers, with notes
- notes and annotations by patent counsel

Having spent the early phases of the FTO analysis with the disciplined rigor laid out in this chapter, the later steps in the FTO analysis should proceed with a minimum of problems. Diligence will pay off in the end with a solid and reliable FTO analysis that can be routinely updated and revised and that can also provide patent counsel with the requisite information for drafting FTO opinion letters. ■

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1 Anonymous. 2004. Freedom to Operate. *WIPO Magazine*, September–October, Issue 5.

2 Woessner WD. 2002. Product Clearance and Noninfringement Opinions in a Post-Festo World. *PLI/Pat* 715: 135–66.

3 Kowalski SP and RD Kryder. 2002. Golden Rice: A Case Study in Intellectual Property Management and International Capacity Building. *Risk: Health Safety & Env't* 13: 47–67. www.piercelaw.edu/Risk/Vol13/spring/Kowalski.pdf.

4 Burrone E. New Product Launch: Evaluating Your Freedom to Operate. The World Intellectual Property Organization. www.wipo.int/sme/en/documents/freedom_to_operate.html.

5 Kryder RD, SP Kowalski and AF Krattiger. 2000. The Intellectual and Technical Property Components of Pro-Vitamin A Rice (Golden Rice): A Preliminary Freedom-to-Operate Review. Brief No. 20, ISAAA: Ithaca, NY. www.isaaa.org/kc/bin/isaaa_briefs/index.htm.

6 Valoir T. 2005. Look Before You Leap: Investing in a Freedom-to-Operate Patent Review. *Executive Legal Advisor,* January 20–21. www.bakernet.com/BakerNet/Resources/Publications/Recent+Publications/FTO+Paper.htm.

7 Wagner JF. 2005. Protection from Discovery of Attorney's Opinion Work Product under Rule 26(B)(3), Federal Rules of Civil Procedure. *American Law Reports Federal* 84: 779–801.

8 Kowalski SP, RV Ebora, RD Kryder and RH Potter. 2002. Transgenic Crops, Biotechnology and Ownership Rights: What Scientists Need to Know. *Plant J.* 31: 407–21. www.blackwell-synergy.com/links/doi/10.1046/j.1365-313X.2002.01367.x.

9 Aljalian NN. 2005. The Role of Patent Scope in Biopharmaceutical Patents. *B.U. J. Sci. & Tech. L.* 11:1–76.

10 Mireles MS. 2004. An Examination of Patents, Licensing, Research Tools, and the Tragedy of the Anticommons in Biotechnology Innovation. *U. Mich. J. L. Reform* 38: 141–235.

11 Xiao J. 2003. Carving Out a Biotechnology Research Tool Exception to the Safe Harbor Provision of 35 U.S.C. §271 (e)(1). *Tex. Intell. Prop.* L. J. 12: 23–67.

12 See *supra* note 9.

13 See *supra* note 10.

14 See *supra* note 10.

15 McCarthy JT, RE Schechter and DJ Franklyn. 2004. *McCarthy's Desk Encyclopedia of Intellectual Property, 3rd edition.* The Bureau of National Affairs: Washington, DC.

16 Simpson PM. 1998. Use of Bailment in Transferring Technology from a University. *Journal of the Association of University Technology Managers* 10: 85–100.

17 Goldstein B. 2002. Overview of Technology Development. *Introduction to the Principle and Practice of Clinical Research* (ed. John Gallin) pp. 307–27. Academic Press.

18 Gardner BA, ed. 1999. *Black's Law Dictionary*. West Group, St. Paul, MN.

19 Schwaller M. 2004. Uniform Biological Material Transfer Agreements: An Argument for Uniform Use. *Hous. Bus. & Tax. L.J.* 4: 190–230.

20 Rodriguez V. 2005. Material Transfer Agreements: Open Science vs. Proprietary Claims. *Nature Biotechnology* 23: 489–91.

21 Houser D. 1993. Exemptions under Patents and Certificates Covering Plants and Comments on Material Transfer Agreements. In *Intellectual Property Rights; Protection of Plant Materials* (eds. SP Baenziger, RA Kleese, and RF Barnes) pp. 107–109. Crop Science Society of America: Madison, WI.

22 See *supra* note 20.

23 Janis MD and JP Kesan. 2002. Plant Variety Protection: Sound and Fury? *Hous. L. Rev.* 39: 727–78.

24 Binenbaum E, C Nottenburg, PG Pardey, BD Wright, and P Zambrano. 2003. South-North Trade, Intellectual Property Jurisdictions, and Freedom to Operate in Agricultural Research on Staple Crops. *Econ. Devel. Cult. Change* 51: 309–35.

25 See *supra* note 18.

26 Wright BD. 2002. Biotechnology and Intellectual Property. In *California Council on Science and Technology, Benefits and Risks of Food Biotechnology*. Chapter 8. July, pp. 151–65.

27 See *supra* note 15.

28 Daniels TP. 2003. Keep the License Agreements Coming: The Effects of J.E.M. AG Supply, Incorporated V. Pioneer Hi-Bred International, Incorporated on Universities' Use of Intellectual Property Laws to Protect Their Plant Genetic Research. *B.Y.U. Educ. & L.J.* 2: 771–813.

29 Koo B, C Nottenburg and PG Pardey, 2004. Plants and Intellectual Property: An International Appraisal. *Science* 306: 1295–1297.

30 Fowler C. 2004. Accessing Genetic Resources: International Law Establishes Multilateral System. *Genet. Resour. Crop Ev.* 51: 609–20.

31 Benda S. 2003. The Sui Generis System for Plants in Canada: Quirks and Quarks of Seeds, Suckers, Splicing, and Brown Bagging for the Novice. *Canadian Intellectual Property Review* 20: 323–80.

32 See *supra* note 30.

33 Brush SB. 2005. Protecting Traditional Agricultural Knowledge. *Wash. U. J.L. & Pol'y* 17: 59–109.

34 See *supra* note 31.

35 Ducor P. 1999. Research Tool Patents and the Experimental Use Exemption: A No-Win Situation? *Nature Biotechnology* 17: 1027–28.

36 Hoffman DC. 2004. A Modest Proposal: Toward Improved Access to Biotechnology Research Tools by Implementing a Broad Experimental Use Exception. *Cornell L. Rev.* 89: 993–1043.

37 See *supra* note 10.

38 *Pioneer v. Holden*. 35 F.3d 1226, 31 U.S.P.Q. 2d 1385 (8th Cir. 1993).

39 Agris, CH. 1999. Intellectual Property for Plants. *Nature Biotechnology* 17: 197–98.

40 Ibid.

41 See *supra* note 39.

42 See *supra* note 30.

43 See *supra* note 31.

44 Woessner WD. 2003. Patent Infringement and Freedom-to-Operate Opinions. *PLI/Pat* 761: 99–132.

45 See *supra* note 2.

46 See *supra* note 2.

47 See *supra* note 11.

48 The World Health Organization Immunizations, Vaccines, and Biologicals. 2004. In *Intellectual Property Rights and Vaccines in Developing Countries*. Meeting report, April 19–20. www.technet21.org/whodocs.html.

49 See *supra* note 6.

50 See *supra* note 19.

51 See *supra* note 24.

52 www.nal.usda.gov.

53 www.google.com.

54 www.biosis.com.

55 www.isinet.com.

56 www.cabi.org.

57 See, also in this *Handbook*, chapter 14.3 by H Thangaraj, RH Potter and A Krattiger.

58 www.uspto.gov.

59 www.espacenet.com/access.index.en.htm.

60 www.delphion.com.

61 Information graciously provided by Kathy Little (Thomson Scientific).

62 Derzko NM. 2005. The Impact of Reforms of the Hatch-Waxman Scheme on Orange Book Strategic Behavior and Pharmaceutical Innovation. *IDEA* 45:165–265.

63 Anderson DZ. 2003. New Orange Book Listing Requirements: Will FDA Raise Bar on Generic Drug Entry? *Lawyers J.* 5: 6–7.

64 Wharton JS. 2003. "Orange Book" Listing of Patents under the Hatch-Waxman Act. *St. Louis U. L.J.* 47:1027–63.

65 See *supra* note 2.

66 www.fda.gov/cder/ob/default.htm.

67 See *supra* note 2.

68 O'Neil MJ, A Smith, PE Heckelman and S Budavari (eds.). 2006. *Merck Index: An Encyclopedia of Chemicals, Drugs, & Biologicals*. Merck & Co: Rahway, NJ. library.dialog.com/bluesheets/html/bl0304.html and www.merckbooks.com/mindex/.

69 See *supra* note 2.

70 See *supra* note 15.

71 See *supra* note 15.

72 See *supra* note 15.

73 See *supra* note 6.

74 Berliner BM. 2004. Preparing Patent Infringement and Freedom-to-Operate Opinions. *Computer & Internet Law* 21: 1–8.

75 See *supra* note 6.

76 Deveau T, and M Hall. 2002. Noninfringement and Freedom-to-Operate Opinions. *PLI/Pat* 715: 115–33.

77 See *supra* note 15.

78 Watase R. 2002. The American Inventors Protection Act of 1999: An Analysis of the New Eighteen-Month Publication Provision. *Cardozo Arts & Ent. L.J.* 20: 649–84.

79 Sullivan RC. 2001. Intellectual Property Due Diligence. AUTM 2001 Annual Meeting, New Orleans, Louisiana, March 2. www.darbylaw.com/Files/tbl_s31Publications/FileUpload137/1629/Autmrcs.ppt.

80 Martinez de Andino JM, RL Tate and T Maddry. 2004. Conducting an Intellectual Property Due Diligence Investigation. *J. Proprietary Rts.* 8: 1–6.

81 Ibid.