How to Conduct a Freedom-to-Operate Analysis for a Drug Repurposing Project

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ABSTRACT

This document provides the general methodology and specific resource access points for performing a Freedom-to-Operate (FtO) analysis tailored to the needs of a drug repurposing project. It has been deliberately written to be performed with minimal technical resources: Only web access is required, and no use is made of artificial intelligence tools. It can be performed by the inventors, up to the point where potentially critical findings (if any) are discussed with a patent attorney. When done properly, this method actually improves the relevance of the analysis, since no patent specialist can be expected to be fully familiar with all the scientific aspects of a repurposing project.

While patent searches are the dominant motive, there is also discussion of how to recruit suitable suppliers, an issue that is particularly important when the compound is reformulated (as will be the case in most cases).

KEYWORDS

drug repurposing; intellectual property; patent searches; freedom to operate.

INTRODUCTION

Drug development never takes place in a vacuum; rather, it must navigate a highly structured environment driven not only by medical science, regulatory affairs, and market dynamics but also by a complex matrix of existing intellectual property (IP) rights, of which patent rights are by far the most important. From an IP perspective alone, the purpose of an FtO analysis is to determine the ability to proceed with the research, development, and/or commercial production of a new product or process with minimal risk of infringing the unlicensed tangible IP rights of third parties. A properly performed FtO analysis that reveals no collisions minimizes the risk that a product cannot be used, sold, offered for sale, or exported.

FtO is even more challenging in the context of drug repurposing, which by definition involves only known active pharmaceutical ingredients (APIs) for which IP protection may still be in force. In addition, drug repurposing requires physical access to the drug or its API to be redeveloped for a new therapeutic use. FtO therefore also requires determining if and where a suitable approved and marketed drug containing the API can be obtained. Alternatively, if no such drug is available, or if the API is to be reformulated for clinical trials, an FtO analysis must also determine if and where the API can be reliably sourced in a quality that meets current Good Manufacturing Practices (cGMP), or if it can be made cGMP compliant.

There are other indirect issues that can affect FtO, such as whether the API is involved in critical litigation or has deeper legal ramifications that may make it inadvisable to reuse it. Such issues are only briefly touched upon as they are beyond the scope of a general FtO analysis guideline.
Basic Tenets

The FTO analysis should be performed at the earliest meaningful stage, ideally as soon as the API(s) to be repurposed, the new therapeutic target indication, and possibly the intended dose and formulation have been defined. It should precede any substantial investment in a repurposing project.

a) An FTO analysis has a limited objective, usually a specific project milestone that defines a decision point, e.g., the drug presentation to be developed, whether a specific risk exists, or whether FTO exists in certain regulatory jurisdictions. It can never be open-ended or all-encompassing in the sense that it assesses all conceivable project risks around the world or indicates potential future business risks that have no immediate basis in current facts. Suitable FTO analysis objectives would be, e.g., “Could we use this particular new formulation?”, “Are there existing rights to this particular combination of drugs?”, or “Do we have clear and imminent obstacles in the seven major pharmaceutical markets?”

b) Only claims matter for FTO. Statements made elsewhere in a patent document are of no concern unless covered by a formal claim in the claims section, even though they may compromise novelty for your own patenting (see “Tenet f” below).

c) No FTO analysis can be proven to be complete, because no search of any kind can be strictly proven to have uncovered all hits (incompleteness theorem). In patent searches, this is exacerbated by the fact that granted claims can be very broad, especially in older patents (e.g., “inflammation” or “autoimmune disease” may be used as a catch-all phrase). So-called Markush structures (drawn chemical structures in which core moieties carry substituents R1, R2, etc. which are broadly defined) are often used to claim ranges that could implicitly cover hundreds of specific compounds. Such claims cannot be properly searched for coverage of a specific compound. For all intents and purposes, an FTO analysis will most likely aim for a “good enough” level of completeness as defined by project-specific parameters.

d) An FTO analysis is a snapshot and is strictly valid only at the time the searches were performed. It requires regular updates at intervals that depend on the dynamics of the searched matters. As a new relevant IP is published, earlier priority dates may be revealed that interfere with the project plan. Because of the nominal 18-month “dark period” between filing and publication, a previously unknown IP may, in the worst case, take precedence over the developer’s own IP.

e) An FTO analysis does not provide risk mitigation measures; it only provides the basis for their development, if any.

f) An FTO analysis is not a patentability evaluation. While it will uncover the cornerstones of the IP landscape in question, its objective is not to outline paths by which the developer might attempt to establish his own IP to protect the repurposed product. It is focused on identifying obstacles, not opportunities.

METHODOLOGY

This section indicates resources and methods that a developer of average knowledge in medicine and pharmacology (roughly corresponding to the graduate student level) can readily use to:

a) conduct a basic FTO analysis for a particular compound in a new therapeutic indication, using only generally available online resources;

b) assemble the results into a data body and an actionable report that forms the basis for an extended FTO analysis involving patent attorneys, legal experts, and business developers; and

c) leverage the results of the FTO analysis for executive decisions concerning the repurposing project, such as prioritization of available alternatives, pursuit of specific presentations for the envisaged repurposed drugs, and similar matters.

The methodology is intentionally limited so that the analysis can be performed by anyone familiar with the science of the intended repurposing project, who has access to the Internet, and who has a basic understanding of how patents are written and how their claims can be interpreted. Access to advanced search and interpretation technologies, such as the burgeoning field of patent informatics, is not required—although it can certainly be employed to enhance the approach outlined here.

The central online tool is PatentScope, the free database provided by the World Intellectual Property Organization (WIPO), and can be found at https://patentscope.wipo.int/search/en/search.jsf. PatentScope contains all international patent applications published by the WIPO, including the examiners’ search reports and other ancillary documents, and also the patents published by the signatories of the Patent Convention Treaty (PCT). It provides access to the full contents of patents and patent applications published by all major national and regional patent offices. Integrated online translation is available, and there is also a cross-lingual expansion mode (CLIR) that can be run in supervised mode to search in different languages.

Numerous tutorials can be found at https://patentscope.wipo.int/search/en/help/tutorial.jsf, and frequent webinars are being held that allow users to make the most of PatentScope. A current list of the contracting states can be found at https://www.wipo.int/pct/en/pct_contracting_states.html.

The patent databases at the European (https://worldwide.espacenet.com/) and US (https://ppubs.uspto.gov/pubweb-bapp/) patent offices can occasionally provide additional specific resources.

The method described here assumes that the FTO focus is on the United States and Europe, which will provide sufficient guidance in most cases since all major pharmaceutical markets except Japan are included. Searching for documents that do not have English claims and/or use non-Latin alphabets would be very difficult. However, it is hardly necessary because patents that do not develop into US and/or European equivalents are rare and in most cases would not be critical.
CONDUCTING PATENT SEARCHES: COMPOUNDS AND DISEASES

Preface

The search methodology described below is the result of many FtO analyses. It should not be considered absolute; rather, it can be varied in innumerable ways, provided that the searching and narrowing of hits is done with a clear understanding of what can and cannot be accomplished by searching and filtering. In particular, files and folders can be named in any other way that preserves how the respective files and collections were obtained.

Stepwise Description of Searches

Step A. Access the PubChem chemical database (https://pubchem.ncbi.nlm.nih.gov/) and search for the API by international nonproprietary name, chemical name, or drawn chemical structure (an editor is provided). Most likely PubChem will return several hits. Ascertain that the suggested best fit result displayed on top represents your API, without additions such as counterions, etc. Note the IUPAC (International Union of Pure and Applied Chemistry) name and the synonyms in the title line. Clicking on the highlighted name will return a very long scrollable list. Copy the Patents section, especially the identifier-supplied patent identifiers (which can be downloaded separately) and the PatentScope link which will look as follows:

https://patentscope.wipo.int/search/en/result.jsf?inchikey= [...] where the InChiKey is the machine-readable string representation of the chemical structure (e.g., in the arbitrarily chosen case of 4-aminopyridine, NUKYPUAOHBNCPY-UHFFFAOYSA-N).

Step B. Click on the link containing the InChiKey provided in (Step A) to conduct a structure search in PatentScope. You will be presented with an analysis page that allows you to set filters for important patent offices including Europe, the United States, and Japan; for international patent codes (IPCs); and for publication years going back to 2013. Set the IPC filter to A61P (which covers “therapeutic activity of chemical compounds or medicinal preparations”). Set the “Countries” filter to “PCT” and the “Year” filter to 2013. You will be presented with a list of international patent applications published in 2013, which will mostly have 2011 priority dates.

Step C. Click on each of the listed patent identifiers, then click on the claims tab. For each PCT patent document, create an empty ASCII text file [API]-WO[numberstring]-claims.txt. (For European and US documents, replace “WO” with “EP” and “US,” respectively.) For non-English claims, use the WIPO Machine Translation option on the upper right corner of the displayed patent text. If the claims contain drawn chemical structures, use your word processor instead of the ASCII text editor. Copy the entire claims list into this file and save. Collect all files into a folder [API]-by-structure_[earliest year]-[present]. Add a text file specifying the date of the search and the search history. Repeat this process for each year up to the present.

Note: We recommend not using cloud services that store data outside the European Union (EU), or are managed by non-EU companies.

Step D. Search the self-created claims files in the “[API]-by-structure_[earliest year]-[present]” folder for your API name, using any synonyms acquired in Step A. For large numbers of files, use a desktop search tool such as DocFetcher (https://docfetcher.sourceforge.net/en/index.html), a free open-source software available for Windows, Linux, and Mac OS. Manually search the word processing files from Step C that did not return text hits; they may contain relevant drawn structures. Copy files with API search hits into a new folder [API]-by-structure_[earliest year]-[present]_API-in-claims.

Step E. Manually search the files with hits that were obtained in Step D for mentions of the disease you want to repurpose your compound for. This requires some judgment. Before starting, make yourself aware of all common names and synonyms of the target condition (e.g., “neuropathy,” “neuropathic pain,” etc.). Mark not only the claim files that directly mention such names, but also those mentioning the corresponding umbrella categories (e.g., “nerve damage” or “nerve trauma” in the above example). Apply this liberally: if you want to redevelop, e.g., for cardiac valve calcification, also mark files containing “heart disease”; if for mild cognitive impairment, also mark files with “dementia” in the claims. Copy these files into a new folder [API]_FtO_focus-files1.

Step F. Go to the PatentScope main search page and download the corresponding whole-patent PDFs for each document in the [API]_FtO_focus-files1 folder. Name these [API]_WO[numberstring].pdf (alternatively, [API]_EU[numberstring] or [API]_US[numberstring] for European and US documents, respectively) so that they will appear adjacent to their respective claim text files when you put it into the [API]_FtO_focus-files folder. For each entire patent document to be downloaded, also go to the “Patent Family” tab and download any European and US document listed there. (With recently published PCTs, this tab will be grayed out.) Name the PDFs [API]_WO[string1]-EP[string2] and [API]_WO[string1]-US[string2], respectively. Put these too into the [API]_FtO_focus-files1 folder where they will associate with their marked claims files.

You now have a set of patent documents that are very likely to raise red flags with your FtO. But these documents only go back 10 years (while patent protection lasts 20 years) and may not include the latest national or regional publications. They also do not include the (relatively few) patent applications that did not go through the WIPO PCT publication process, and they rely on proper indexing of your compound’s chemical structure, which may not always have been done. Copy them to a new folder, retaining the earlier one.

Step G. To complete your search, go to the PatentScope structured search page: https://patentscope.wipo.int/search/en/structured-Search.jsf.
From the top menu, click on “Search” and select “Field Combination.” Using the dropdown menus, create a Boolean query that searches for your compound (connect all alternative names with OR in brackets) in English claims, using International Class (A61K OR A61P). Under “Offices,” select “United States of America” and “European Patent Office.” Leave the defaults for language (English) and stemming. Depending on your compound, this can create a very long multipage list of documents that are listed with their abstracts. You need the claims sections of all of these; proceed as under Step C while selecting “Pub Date Desc” as the sort order. You do not need to go back further than 20 years from your current year. Then proceed onward to Steps D through F. Put the resulting files in a new folder [API]_FtO_focus-files2. Meanwhile keep the [API]_FtO_focus-files1 folder open in a separate window while repeating Step F; you do not need to download the European and US documents that are already in there.

Evidently this will create many duplicates. The reason why years from 2013 onward are included although they have been searched before is that this creates an orthogonal search that makes sure that all relevant European and US documents published during these recent years have been captured. Expanding the IPC to A61K serves a similar purpose. You will likely notice several additions to the original search results. The capture phase is now complete.

**Step H.** Create a new folder [API]_criticalpatents. From both [API]_FtO_focus-files folders, move those European PDFs that have “B” annexes, and those US PDFs that only have a seven-digit number without a year prefix, into this new folder which will then contain only issued patents. These will be most critical for FtO and will be examined first.

Then create a folder [API]_criticalapplications, and move those European PDFs that have “A” annexes and those US PDFs that only have a 11-digit number (the first four being a year prefix) into this folder. Finally, move those PCT documents that contain both compound and new use in the claims but have no European and US equivalents yet—those that have been downloaded in (Step F)—into the [API]_criticalapplications folder. This folder then contains documents with critical claims that have not yet been granted (and might be deleted during the procedure of granting or rejecting the respective patent application). These will also be examined, and their progress closely monitored.

**ASSESSING CRITICAL PATENT DOCUMENTS FOR FtO**

Now comes the most important part: the examination of the claims section of the documents selected by the search. A brief digression is required here to illustrate the general principles of how this section is structured.

At first glance, patent claims appear to be just a collection of numbered paragraphs, but in fact they form a hierarchically structured body that develops the claims from one or more independent claims (which may be written in very general terms) to dependent claims, which may be cascaded and use increasingly specific wording. Because this resembles multiple branches from one or more roots, the entire body of claims is aptly called a “claim tree.” (One of the essential skills of a good patent attorney is to construct this “tree” in such a way that dependent claims can be surrendered to the patent examiner’s demands while retaining the broadest protection possible.) Dependent claims are instantly recognizable by their references to claims higher in the hierarchy. The best way to deconstruct the structure of a claim tree is to visualize it—in fact, draw it—as a tree (this may sound complicated, but it is actually a matter of minutes) (Figure 1).

Study each document in the [API]_criticalpatents folder (or each such pair if paired European and US patents exist), and sketch the claim trees. (You will note that the claims sections might differ for EU–US pairs depending on which claims have been granted while the body text will likely be the same.) If you identify a claim containing your particular candidate compound, walk upwards through the claim tree until you reach the independent “root” claim to see if it remains critical in your opinion. (For example, this would no longer be so if you want to repurpose a compound with known activity “X” for your newly discovered activity “Y,” while the root claim refers to it only as having activity “X.”) In the body text, identify any biological data (human, animal, cell, or tissue culture, cell-free assay data) that support the claims conflicting with your FtO and discuss them in your summary. Repeat this process with the [API]_criticalapplications folder (see Figure 2 for a flowchart representing the entire search and evaluation process).

Sit down with a patent attorney who specializes in the pharmaceutical field, with clear instructions to base the requested opinion only on the information you provide. To avoid the cost of additional searches by the patent attorney to support his or her opinion, provide copies of your files to the patent attorney, noting the documents you consider most critical. The attorney may discover additional aspects that you have overlooked, but may also indicate that some of your concerns are not as critical as you think.

An initial executive decision can now be made as to whether the project should proceed based on the IP environment with respect to the API in its intended new use. This decision will take into account several additional issues. If FtO-preventing patents are about to expire, the project may not only be feasible (considering development times) but may even be attractive if the interest of the original developer can be aroused.

**ASSESSING PRESENTATIONS AND DOSES**

Especially when generic APIs are repurposed, new drug formulations with different loading doses and release characteristics need to be developed to optimally adapt the API to the new treatment modality and to prevent competition. The search method described here cannot be readily applied to identify existing IP that conflicts with such development intentions. Drug delivery is a highly specialized field with its own specialized developers and unique IP challenges. In this respect, the possibility of new patenting—i.e., a patentability assessment—will usually take precedence over FtO.

**SECURING SUITABLE SUPPLIERS**

Although this is often not considered part of an FtO analysis in the classical sense, but rather as a regulatory matter, the next
critical FtO step is to ensure that either a finished drug product marketed in the EU or the API is available in cGMP quality. The inability to purchase sufficient quantities of the API from a supplier with a valid GMP certificate or (if outside the EU, except for the USA and Switzerland) an EU Written Confirmation (EU-WC) certifying that the manufacturing site complies with cGMP according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q7 guidelines means that clinical trials with a reformulated formulation would not be allowed. While in principle a non-GMP API could be reformulated in a GMP facility to make it GMP compliant, this introduces another round of bureaucracy and should only be considered as a last resort.

There is a high probability that a simple web search for suppliers of your API will return a multitude of (mostly Asian) vendors who guarantee GMP and ICH Q7 quality (which may well be true), but upon persistent inquiry turn out to be unable to provide the appropriate certifications. The best way to obtain a first orientation

Figure 1. A typical claim tree for a drug repurposing patent. Claims #1 and #19 are independent ("root") claims; claims #2 through #18 are dependent forming the "claim tree."
of fully compliant vendors is to access the PharmaCompass website at https://www.pharmacompass.com/find-suppliers, look up your API, and apply filters to look for manufacturers who have either have a European or US Drug Master File or an EU-WC in active status. The cGMP status of European manufacturing sites can be confirmed at the EudraGMP database at http://eudragmdp.ema.europa.eu/inspections/gmpc/searchGMPCompliance.do. Your regulatory department will take care of further details.

Determining whether a technically suitable supplier has a good reputation or may be involved in pending litigation that could affect its ability to supply the drug or API can initially be attempted through careful web searches, but may require expert legal assistance to identify, confirm, and evaluate. Because supply contracts will not be in place during early repurposing efforts, developers should purchase sufficient finished drug products or their APIs for each clinical trial. Of course, it is also a good idea to make a test purchase from an alternative supplier.

The field is now prepared for a final decision on the repurposing project.

**ASSESSING Fto FOR DRUG COMBINATIONS**

If the new product to be developed contains two or more to-be-repurposed APIs, all steps described in the sections below Methodology must be performed for each API, even if only the combination of APIs is intended to provide the desired repurposed therapeutic effect. In addition, it will be necessary to consider whether the specific combination is still under exclusivity for the intended use. Patents very often contain boilerplate language for most combinations with “excipients”; in most cases, such combinations have never been tested, but may have found their way into

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**Figure 2.** Simplified flowchart for a patent search intended for a drug repurposing Fto analysis. API, active pharmaceutical ingredient; Fto, Freedom-to-Operate; IPC, international patent code.
granted claims, either as a named compound in a list or even as a therapeutic class, which is particularly dangerous.

There is no shortcut to performing these multiple FtO analyses, and the workload can be substantial.

CONCLUSIONS
Conducting an FtO analysis before committing significant resources to a repurposing project is essential to the developer’s ability to make an executive decision about whether the project should be undertaken at all, at least in its intended form. We have provided a general outline of an FtO analysis process that can be conducted without resorting to patent informatics or wholesale outsourcing to patent attorneys, who in most cases would not be as familiar with the details of the applicable science as the developers. Instead, we provide the means to perform an FtO analysis using only commonly available technical means that can be done internally until the potential results can be discussed with a patent attorney. The overall impact and relevance is that academic repurposers and start-up companies can use this as a tailored part of the REPO4EU drug repurposing platform that provides specific and well-informed decision points early in any repurposing project.

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The author declares no conflict of interest.

DATA AND CODE AVAILABILITY
Data and code availability does not apply.

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REFERENCES
There are no references.