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The Guide to Life Sciences: Key issues for senior life sciences executives

2024

A deep dive into patent law and exclusivity in the United States

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The fourth edition of the Guide to Life Sciences delivers key analysis designed to help senior life sciences executives better understand the strategic and legal IP challenges that they face around the world. This specialist intelligence will help them to protect, enforce and monetise the IP rights that are so crucial to businesses in the space.

Generated: June 26, 2024

A deep dive into patent law and exclusivity in the United States

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Summary

INTRODUCTION

The pharmaceutical industry is critical to the progress of science in researching, developing and introducing new therapies that improve the health and quality of life for patients around the globe. This continued progress requires an extensive amount of funding and financial risk due to the complexity and unpredictability of basic research, clinical trials and the approval process, which result in many failed drugs for every success. It is estimated that it takes about 10 to 15 years, with an average cost of US$1–2 billion, for each new drug product to be approved for therapeutic use (D Sun, W Gao, H Hu, S Zhou, Why 90% of clinical drug development fails and how to improve it?Acta Pharm Sin B 2022, 12(7):3049–62). Accordingly, exclusivity – provided by a robust patent portfolio and regulatory statutes – is essential in order to recoup the massive investments incurred during research, development and regulatory approval of pharmaceutical products. These exclusivities are also critical in providing and maintaining resources for the further development of other therapies in a company's pipeline.

Unlike many other industries, the filing and development of a pharmaceutical patent portfolio with the United States Patent and Trademark Office (USPTO) most often occurs concurrently with a long and protracted process before commercialisation can occur. The process includes initial research and development and pre-clinical and clinical trials and culminates with the filing of an application for regulatory approval with the United States Food and Drug Administration (FDA). A US patent expires 20 years from the earliest filing date, not including certain statutorily available extensions. Therefore, it is not uncommon for a patent to be in force and losing valuable patent term while the subject matter of the patent is being developed and under regulatory review. It is also not uncommon that, upon drug approval, the underlying patent has expired or has only a fraction of its available term available.

Unfortunately, this often results in the discontinuation of programmes that could have otherwise provided great benefit to many patients. These inequities, among others, were mitigated by passage of The Drug Price Competition and Patent Term Restoration Act, better known as the Hatch-Waxman Act. The Hatch-Waxman Act provides incentives for the development of new innovative pharmaceutical products, as well as an abbreviated pathway for generic manufactures to bring lower-cost versions to market.

The timelines of both patent prosecution and regulatory approval should never be viewed as two separate and distinct exercises. Statements made to the FDA should always be consistent with statements made to the USPTO as unintentional inconsistencies could result in difficulties with the eventual enforcement of a patent. Likewise, the dates related to patent filing and patent term expiration intertwine with actions and exclusivities related to regulatory approval as promulgated by The Hatch-Waxman Act.

There are many pitfalls in the developmental timeline of a pharmaceutical product, from initial identification of a candidate to post-marketing launch. Not having a well-thought-out strategy can make a significant difference in the result: the approval of a beneficial medicine with strong exclusivity as opposed to an aborted launch or a relatively short exclusivity with quick generic entry. Having a keen understanding of the intricacies of US patent law and its interplay with regulatory provisions is key to navigating the many minefields inherent in the ultimate commercialisation of a successful product.

PECULIARITIES OF US PATENT LAW

When a pharmaceutical company first identifies and designates a new molecular entity as a developmental candidate for the pursuit of regulatory approval, immediate consideration must be given to filing a patent application in order to initiate the process to secure exclusivity. This is particularly important in light of the conversion of the US patent system from a 'first to invent' system to a 'first to file' system in 2013 under the Leahy-Smith America Invents Act (AIA). In the highly competitive landscape of the life sciences industry, sometimes filing a patent application even one day earlier can prove to avoid 'prior art' such as a journal publication or a patent application of a competitor being citable against the application, which could negatively impact the possibility of obtaining meaningful patent claim scope.

When filing an initial patent application for a new molecular entity, all in-vitro and in-vivo studies have not yet been performed. In many cases, these studies provide important data to support a comprehensive patent application. In this situation, the filing of a provisional patent application with the USPTO under 35 US Code § 111(b) may help to mitigate this issue. This type of filing – unique to the US patent system – provides a low-cost way to establish an earlier filing date with less formal requirements. A US provisional application does not get examined, nor does it issue as a patent; rather, it is a placeholder to obtain a filing date that acts as the cut-off for the availability of prior art that could be available for citation against the subject matter of the application. To maintain the filing date of the provisional application, a non-provisional or 'utility' application with a claim of priority to the earlier date must be filed within 12 months. The utility application then undergoes formal examination with the hope of issuance as a US patent.

Beyond offering lower cost and less preparation time than a utility application, a US provisional patent application provides other benefits, such as the ability to add further disclosure, examples and data to the application while preparing the non-provisional application claiming priority to the provisional application. The provisional application also allows the establishment of a priority date before the generation of all data that may be desired to be included in the application.

A common misconception when claiming priority to a provisional application is that all of the subject matter in a later non-provisional patent application is entitled to the provisional filing date. However, a provisional application only provides priority support for the disclosure that is actually contained in the document. Any additional disclosure that is included in a non-provisional application is only entitled to the non-provisional filing date and will not enjoy the benefit of the provisional filing date. For instance, if a provisional application discloses that Compound X is suitable for the treatment of asthma but does not include a dosing range for human subjects, the later disclosure of the dosing range in a later non-provisional application would not have the benefit of the earlier date. A claim to the dosing range in the non-provisional application would be susceptible to intervening prior art that was known after the provisional filing date but before the non-provisional filing date. Therefore, it is always good practice to prepare and file as robust a provisional patent application as possible based on the knowledge and data available at that time. This maximises the probability that the provisional application will provide a strong priority date.

The other benefit of utilising provisional patent applications is maximising patent term. The statutory patent term of a US patent is 20 years from the earliest non-provisional filing date. Provisional patent applications are not part of the patent term calculation. Therefore, a priority date can be established with the filing of the provisional patent application but the

patent term will not start to run until after the non-provisional application is filed up to one year later. This allows up to a 21-year period from the provisional filing date to the end of the patent term. If a utility application is filed without first filing a provisional application, the 20-year term will expire up to one year earlier. Utilisation of provisional applications will necessarily delay the examination and grant of the patent application. However, as pharmaceutical products are subject to regulatory approval and are not being marketed at early periods of the patent process, this delay in examination and grant will not typically have any commercial effect and is outweighed by the later expiring patent term provided by the utilisation of provisional applications.

Another important distinction between US patent law and many other jurisdictions is the availability of a 12-month grace period under 35 US Code § 102 for prior public disclosures by the inventors (or by another party who obtained the disclosed subject matter from an inventor). This allows for the filing of a US patent application up to one year after inventor-related disclosures, including publication of the invention, public use of the invention or a sale or offer to sell the invention, without the public disclosure being available for citation against the patent application as prior art. This differs from many other jurisdictions, which have either (1) a six or 12-month grace period under specific circumstances as prescribed by each jurisdiction or (2) an absolute novelty bar that negates patentability even if the application was filed the next day after any public disclosure related to the inventor. Regardless of the 12-month grace period, patent applicants in the US that plan on filing patent applications outside the US must be conscious of public disclosures in order to preserve their foreign filing rights. At the very least, a US provisional patent application should be filed prior to any inventor-related public disclosures, as most industrialised countries recognise US filing dates in their own countries based on the Paris Convention for the Protection of Industrial Property (1883).

PRODUCT LIFE CYCLE MANAGEMENT STRATEGIES

The identification of a new molecular entity as a developmental candidate is the first step in the development and approval of a pharmaceutical product containing the same. Likewise, the filing of a patent application directed to the new molecular entity should be the first step in a series of newly filed patent applications, with staggered filing dates for each milestone during the developmental process.

It is undoubtably the case that during research and development of a pharmaceutical product, there will be challenges and obstacles that will need to be overcome. Many of the solutions will not be obvious to one of ordinary skill in the art and have the potential to become the subject of a new patent application.

Example fact patterns include the following.

- In-vivo testing demonstrates that a drug has affinity for a particular human receptor and is applicable to treat a disease state. However, the drug is insoluble and has poor or variable absorption, leading to low bioavailability and lack of efficacy. Identification of a new and unobvious polymorph or nano-sized version of the drug that leads to increased solubility and bioavailability is patentable subject matter.
- A drug exhibits a short half-life, is quickly excreted by the body and must be frequently dosed, leading to decreased patient compliance and poor therapeutic outcomes. Identification of a novel twice daily or once daily controlled release dosage form

that overcomes the limitations of the short half-life of the drug is patentable subject matter.

- An acid labile drug cannot be orally administered as it breaks down in the gastro-intestinal system. The identification of a novel and unobvious formulation that can effectively deliver the drug by an alternative route of administration (eg, transdermal or nasal) is patentable subject matter.
- A drug is shown to lack stability and breaks down after short term storage. The identification of a novel and unobvious formulation that includes an inactive excipient that stabilises the formulation (eg, as shown by accelerated storage conditions at high humidity and temperature) is patentable subject matter.
- In-vivo studies showing novel and unobvious pharmacokinetic parameters (eg, maximum plasma concentration (Cmax) or time to maximum plasma concentration (Tmax)) that provide a positive therapeutic plasma drug concentration over time is patentable subject matter.
- In-vivo studies demonstrating a novel and unobvious dose of a drug (eg, mg amount) or dosing regimen (eg, ascending or descending dose) providing an unexpected positive therapeutic outcome is patentable subject matter.
- Research and development showing that a drug initially exhibiting therapeutic use for one indication (eg, nausea) has therapeutic use for an additional indication (eg, antineoplastic) is patentable subject matter.

The series of multiple patent filings provides additional obstacles that a competitor must overcome in the development of an equivalent or similar product and increased value to the company for potential licensing, acquisition or other transaction. However, the greatest benefit of tiered patent filings (ie, a patent filed for each stage of development) is staggered patent term. Each new filing will provide the product with a new 20-year patent term for a longer exclusivity time.

This path must be very strategic as it is possible that the initial or prior filings will have published more than 12 months before the new filing and will have to be overcome as prior art so the new filing can issue as a patent. This is where presentation of the patentability story and how the applicant overcame previously described obstacles can have a great impact on the successful issuance of new patents providing valuable extended term. Data and working examples can be very valuable in establishing patentability (eg, by showing unexpected or surprising results). Thus, it is best practice to include this data in the application. However, under the rules of the USPTO, the data can sometimes be presented by way of an expert declaration, if the new data is based on the teachings of the disclosure present in the application.

When drafting a patent application, in addition to showing utility (ie, use), novelty and non-obviousness, care must be taken that the patent application presents the invention to meet the written description and enablement requirements as codified in 35 US Code § 112, as well as directed to patentable subject matter as codified in 35 US Code § 101.

The written description requirement requires that the patent application be sufficient to demonstrate that the inventor had possession of the invention being claimed at the time of the application was filed. This is most often tested when amendments are made to the claimed subject matter during the examination process. Amendments or new claims that

are made during prosecution that are not supported by the patent specification as originally filed will violate the written description requirement. Accordingly, the application when filed should include disclosures such as alternative embodiments of the invention, materials and components that can be interchanged in the invention and working numerical ranges and parameters that can be varied (eg, percentages of components in a mixture or processing temperature ranges).

The enablement requirement demands that the patent application teaches one of ordinary skill in the art of how to make and use the invention without undue experimentation. In the pharmaceutical arts, this typically takes the form of examples and data. The patent laws also require that broad patent applications must be enabled for the entire breadth of the claims and will typically require more enabling disclosure as compared to a narrower patent claim.

Patentable subject matter is another obstacle an applicant may face when applying for a patent. Patentable subject matter is continuously evolving based on new case law. This is particularly pertinent to natural products and diagnostics. In Alice Corp. v CLS Bank Int'l-, 573 US 208 (2014), the US Supreme Court set forth a two-part test to determine patent eligibility under 35 US Code § 101. Under the test, a patent claim is ineligible if (1) it is directed to a law of nature, natural phenomena or abstract idea and (2) lacks elements sufficient to transform the claim into a patent-eligible application. One example of a transformation of a natural phenomenon to a patent eligible application is a method of treating a disease with a pharmaceutical formulation containing a plant component (ie, a natural product). Although a patent claim to the plant component itself would violate the first step, a claim to the pharmaceutical formulation (ie, the natural product combined with additives) or a claim to a method of treatment would likely overcome the second prong of the test.

NON-PATENT EXCLUSIVITY

Separate and distinct from patent exclusivity is clinical exclusivity granted by the FDA upon approval of new drug applications that rely upon clinical studies. The effect of clinical exclusivity is certain non-patent time limited delays and prohibitions on the FDA approving competitive products. This non-patent exclusivity is granted by the FDA as an incentive to the development of pharmaceutical products that may otherwise not have patent protection (eg, due to patent expiration or statutory bars to patentability), although the FDA will grant clinical exclusivity even if there is patent protection for the approved product or approved method of treatment. The clinical exclusivity term starts to run from the approval date of the pharmaceutical product; therefore, when there is an existing in-force patent encompassing the drug product when the clinical exclusivity is granted, the two terms run concurrently. The clinical exclusivity is not tacked on to the end of the patent term.

Various non-patent exclusivities include New Chemical Entity Exclusivity (five years), New Clinical Investigation Exclusivity (three years), Orphan Drug Exclusivity (seven years) and Pediatric Exclusivity (six months added to existing patents or exclusivity).

Before discussing each exclusivity, it is important to understand various types of drug applications that are filed with the FDA.

- A new drug application (NDA) is an application submitted under section 505(b)(1) and approved under section 505(c) of the Federal Food, Drug and Cosmetic Act (the FD&C Act) that contains full report of safety and effectiveness.
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An abbreviated drug application contains a reference to the clinical studies of the innovative product and takes the form of either an abbreviated new drug application (ANDA) or a 505(b)(2) application.

- An ANDA is an application submitted under section 505(j) of the FD&C Act for a drug product that is considered to be bioequivalent to a previously approved innovator product. The ANDA references the FDA's previous findings that the drug product is safe and effective without the ANDA filer having to provide clinical studies to prove the same. The ANDA needs to show that the submitted product has the same active agent, dose, route of administration, dosage form and conditions for use and is bioequivalent (showing similar blood concentration levels that produce the same effect as the comparator product).
- A 505(b)(2) application is an NDA submitted under section 505(b)(1) and approved under section 505(c) of the FD&C Act that contains full report of safety and effectiveness but references certain findings of a previously approved product. A 505(b)(2) application has the same active ingredient as the innovator product but typically differs by one or more of dosage form, dose or route of administration.
- New chemical entity (NCE) exclusivity is granted based on clinical studies conducted on a compound that was not previously the subject of FDA approval either alone or in combination. The five-year term runs concurrent with any existing patent exclusivity and expires five years starting from the date of approval of the drug product. During this time, the FDA will not accept the filing of an ANDA or 505(b)(2) application referencing the approved product, except that such abbreviated applications may be submitted after four years if they contain a certification of patent invalidity or non-infringement (see below).
- New clinical investigation exclusivity provides a three-year term that the FDA will not approve an ANDA or 505(b)(2) from the date of the exclusivity, for a drug product that contains an active moiety that has been previously approved, when the application contains reports of new clinical investigations (eg, directed to new formulations, new routes of administration or new therapeutic indications) that were essential to approval of the application. This type of exclusivity does not block the submission of the abbreviated applications.
- Orphan drug exclusivity is associated with rare diseases that effect fewer than 200,000 people in the US. The increased term is an additional incentive for the development of drugs for these rare disease states. It is a seven-year term that the FDA will not approve any application for the same drug for the same orphan disease, regardless of whether it is a full NDA or an abbreviated application. Orphan drug exclusivity does not bar the FDA from approving the same active agent for a different disease state than the orphan disease.

Paediatric exclusivity does not run from the approval date. Rather it adds term to existing patents and non-patent clinical exclusivity. The term is six months based on the submission of paediatric studies on the active agent in response to a request from the FDA.

Biologicals have a longer term based on the AIA. Upon approval of a biological product, the FDA will not grant the approval of a bioequivalent product for 12 years after approval.

PATENT TERM EXTENSION

Under 35 US Code § 156, there are circumstances when an unexpired patent may receive a patent term extension (PTE) based on regulatory delay of a pharmaceutical product that is the subject of the patent. PTE may only apply to a pharmaceutical product that has never been the subject of FDA approval in any other application. PTE is based on the following calculation:

- PTE = RRP – DD – ½ TP
- RRP is the portion of the regulatory review period that occurs after the issue date of the subject patent. The RRP includes a testing phase (TP) and an approval phase (AP) as defined below.
- DD is the time period during the RRP that the applicant did not act with due diligence.
- TP is the time period during the RRP between the effective filing date of an Investigational new drug application (IND) and the initial submission of a New Drug Application (NDA) (only one-half of this time is eligible for PTE).
- AP is the time period during the RRP between the initial submission of the NDA and the approval of the product.
- An application for PTE must be submitted within 60 days of the approval of the pharmaceutical product by the FDA. A maximum of a five-year term can be restored to a patent under this process, which is subject to the limitation that the total patent life cannot exceed 14 years from the approval date of the product.
- PTE can only be applied to one patent (although PTE applications can be filed for multiple patents and the applicant can then choose the patent that has the most favourable outcome).
- When a PTE application has been made but the patent will likely expire before a final determination is made, the applicant may request one or more extensions of the patent for periods up to one year.

ORANGE BOOK AND HATCH-WAXMAN TIMELINES

A critical strategic goal in portfolio development is the grant of one or more patents that can be listed in the publication Approved Drug Products with Therapeutic Equivalence Evaluations (commonly known as the Orange Book). The Orange Book lists drug products that have been approved on the basis of safety and efficacy by the FDA and lists patents that cover the approved product or method. Composition of matter and method of treatment patents are eligible for listing in the Orange Book. Method of manufacturing patents are not eligible to be listed in the Orange Book.

When a competitor files an ANDA or 505(b)(2) application seeking approval of a generic product, a certification must be made against the patents listed in the Orange Book for the innovator product under 21 US Code § 355. The available certifications are as follows (referred to by the numbered paragraph in the statute):

- Paragraph 1 certification: there are no patents listed in the Orange Book.
- Paragraph 2 certification: the patents listed in the Orange Book are expired.
- Paragraph 3 certification: the generic applicant will wait to market its product until the Orange Book patents expire.
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Paragraph 4 certification: the Orange Book listed patents are invalid, unenforceable or will not be infringed by the manufacture, use or sale of the drug product for which the abbreviated application is submitted.

If a Paragraph IV certification is filed, the generic applicant is required to contact the NDA holder. After notification, the NDA holder has 45 days to initiate a patent infringement lawsuit against the generic applicant under 35 US Code § 271(e)(2)(A).

With initiation of the patent infringement suit, the FDA will initiate a 30-month stay provision. Under this provision, the FDA will not approve the abbreviated application for 30 months. The stay can be shortened by the court in the event that a court finds 'a failure of either the plaintiff or defendant to cooperate reasonably in expediting the action' or a court issues a final order ruling that the patent is invalid, non-infringed or unenforceable.

The 30-month stay is automatic and does not rely upon the NDA holder showing a likelihood of success on the merits. Therefore, obtaining Orange Book listable patents is an important strategy in delaying generic entry.

CONCLUSION

Life Science patent law entails many nuances that must be navigated to create a patent portfolio that enables an innovative company to recoup its investment in bringing new drugs to market and to allow further investment into their new product pipeline. With the proper strategy and implementation of a holistic approach, a valuable patent portfolio can be created to advance human health and wellness.

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