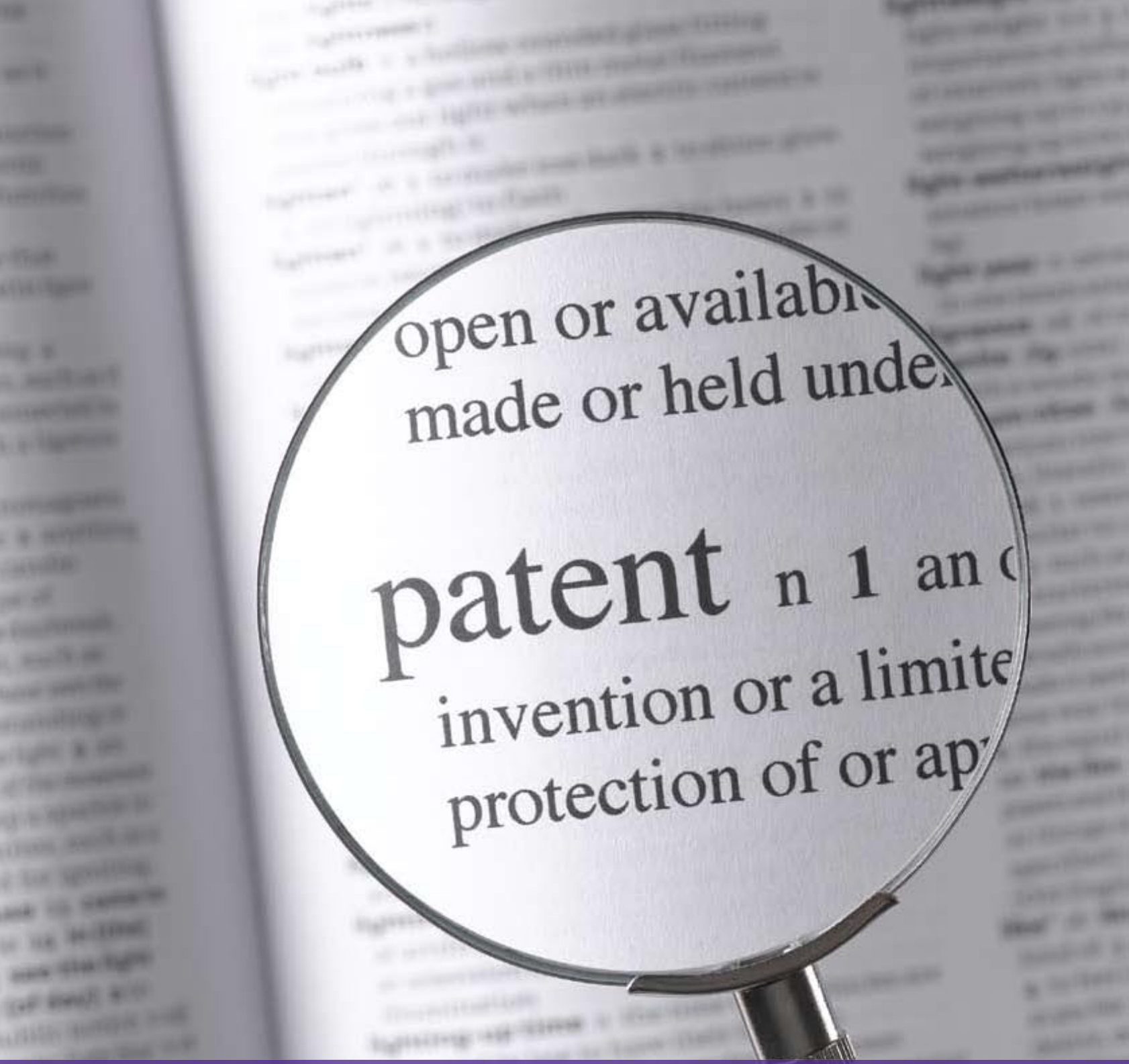


Key Aspects of Pharmaceutical Due Diligence Intellectual Property Assessment—Part I

By Raymond A. Huml, MS, DVM, RAC and Allen R. Baum, JD

Part one of this two part series provides a summary of the key aspects of US and EU patent exclusivity, as well as a discussion of patent exclusivity for the due diligence intellectual property assessment. Part II, to be published next month, will provide an overview of the due diligence process for the intellectual property assessment, highlighting the roles of the regulatory professional, patent attorney and CMC professional. It also will present a case study to tie together the concepts presented in both Parts I and II.

Introduction

The US Patent and Trademark Office (USPTO) defines "patent" as "an intellectual property right granted by the Government of the United States of America to an inventor to exclude others from making, using, offering for sale, or selling the invention throughout the United States or importing the invention into the United States for a limited time in exchange for public disclosure of the invention when the patent is granted."[1] Due to the marketing power provided by patent exclusivity, the intellectual property (IP) assessment has become the linchpin of the due diligence process for product based investing.[2] An accurate view of the patent landscape and regulatory exclusivity surrounding a particular product may be used to better understand risk, forecast revenue, seek price concessions or prepare contract language to mitigate risk.

The strength of a patent, its remaining life and the potential to obtain regulatory exclusivity form the basis for protecting a branded product from competition, including generics. Another key issue is freedom to sell a product without interference from third parties that may own relevant patents. Because regulatory professionals are increasingly being asked to participate on due diligence teams, they need to be familiar with the IP investigational process and the key outputs of the IP assessment. This familiarity leads to a better understanding of the risks associated with the inevitable patent challenges to financially successful branded products and potential threats from third-party patent owners.

This article reviews regulatory legislation enacted to provide additional marketing exclusivity in addition to patent protection. It also presents a due diligence approach that has been used successfully by a CRO partnering entity and that resulted in a commitment of almost $3 billion (US) in capital. Although targeted to product-based partnering investments, this due diligence process could easily be applied elsewhere, for example, to the merger and acquisition environment.

Although IP is respected in major International Conference Harmonisation (ICH) countries (e.g., US, EU and Japan), not all countries honor patent protection equally and this reality must be factored into a global marketing strategy. Moreover, the patent and regulatory exclusivity situation for a given product often varies substantially by country. An unfavorable situation may preclude marketing a product in a particular country.

For purposes of this article, "product" generally refers to small molecules. It does not include biosimilars or optimized follow-on biologic/proteins, which are covered in the recent *Patient Protection and Affordable Care Act* (23 March 2010).[3] "Generic drug application" and Abbreviated New Drug Application (ANDA) are used interchangeably herein. With some exceptions, the same principles apply to 505(b)(2) applications.

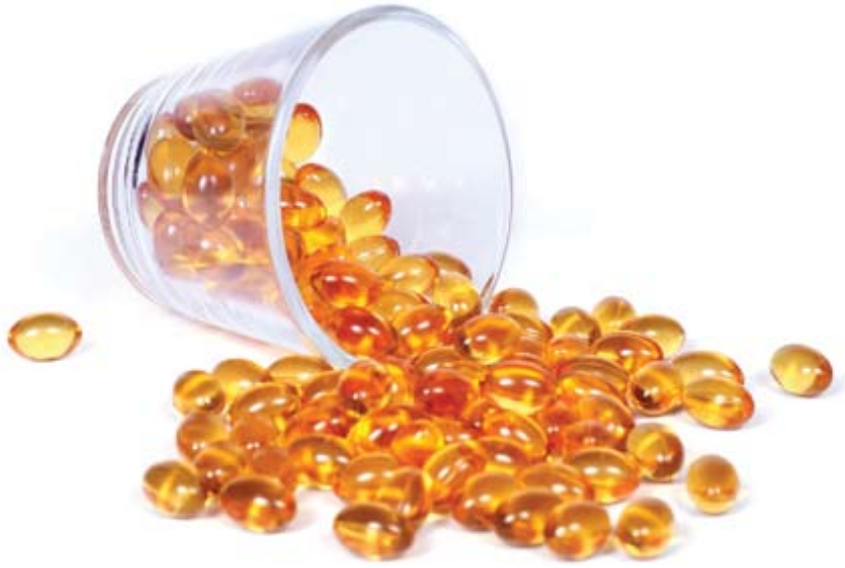
Patent Exclusivity

As new products (and delivery systems, regimens or combinations) are discovered at the chemistry bench or from a successful clinical trial, companies seek to obtain patents to protect their discoveries. The two most common types of patents encountered in the pharmaceutical industry are composition-of-matter (COM), e.g., unique ingredients or older ingredients tweaked in a novel way and method-of-use (MoU), e.g., new methods of treating particular diseases or a different dosing regimen or combination of therapies. Patents are issued in the US if the discovery is deemed useful, novel and non-obvious and meets other guidelines posted on the USPTO website.[4]

There is a lag between submission and approval of a patent application, called the "patent pending" period. Currently, there are more than 700,000 US patent applications that have not yet been examined and a typical application remains pending for 36 months or more. Once a patent has been issued, it protects a pharmaceutical product for 20 years from the date the first nonprovisional patent application was filed unless it is later found invalid or unenforceable by a court. Note that a provisional application may be filed a year earlier to establish a filing date without reducing the patent term. A nonprovisional application begins the examination process since a provisional application does not receive substantive examination by the USPTO.

Since many drugs take 10 or more years to develop, this usually leaves less than 10 years of residual patent exclusivity plus any patent term extension (up to five additional years) to market a product before a generic competitor erodes the brand's sales. This period may be cut short by a successful patent challenge from a generic competitor. Accordingly, it is advisable to conduct an extensive review of potential invalidity challenges as part of the due diligence process when considering a partnership with the owner of a new product. This often entails carefully reviewing the prosecution history of the relevant patent(s) and gathering prior publications and patents to determine the likelihood of a successful patent challenge.

Unsuccessful attempts have been made to unify European patents in the EU (e.g.,



Community patent and the European Patent Litigation Agreement). European patents are currently granted by the European Patent Office—enforced at a national level and issued on a country-by-country basis after examination at the European Patent Office.

At an early stage in the diligence process, the patent attorney (PA) in conjunction with the due diligence team's project leader will determine the basis of the IP protection, including geographies, type of protection (e.g., COM or MoU) and the history of the branded product. With this information and additional research, the PA can make a preliminary determination of the likely term of patent exclusivity and identify potential threats to the exclusivity as well as their timing). Simultaneously, the PA can research whether the current product might infringe other patents owned by competitors or other third parties, and, if so, the potential consequences.

Regulatory Exclusivity and the US *Drug Price Competition and Patent Restoration Act*

Enacted in 1984, the US *Drug Price Competition and Patent Term Restoration Act* (usually referred to as the *Hatch-Waxman Act*), provides a regulatory framework and incentive for generic drug approvals.[5,6,7] The act sought to balance the need for generic drugs with financial incentives for research and development. A key intention was to enable generic drug companies to conduct noncommercial development activities prior to patent expiration of the reference product without fear of infringement while also allowing branded product companies to recoup patent exclusivity time lost during the regulatory approval process. The act provides a mechanism for resolving patent disputes (and risk of exposure to monetary damages) prior to commercial sale of the branded product and gives a 180-day marketing exclusivity period to the first generic applicant that challenges the relevant brand patent. As a result, there are various aspects of the act that impact the period in which an approved brand product will enjoy market exclusivity:

1. up to a five-year extension for an existing innovator patent to compensate for patent term lost during the testing and approval phase (total patent term plus extension is limited to 14 years)
2. a research exemption for patent infringement in conducting work for regulatory approval
3. for New Chemical Entities (NCEs), five years of exclusivity preventing FDA acceptance of a generic drug application, although a generic drug application alleging a listed patent is invalid or not infringed may be filed four years after approval (will run concurrently with patent exclusivity);
4. for new clinical investigations other than bioequivalence studies (e.g., new indication), three years of exclusivity preventing approval of a generic drug application (will run concurrently with patent exclusivity) and an additional six months of exclusivity for pediatric studies tacked onto one of the following: patent term or NCE or new clinical investigation exclusivity (pediatric exclusivity is provided under the *Food and Drug Administration Modernization Act of 1997*)
5. 30-month preclusion of ANDA approval due to ongoing patent litigation, opportunities to challenge the validity of patents issued to innovator drug companies and exclusivity for the first approved generic application that prevents approval of a subsequent generic drug application for 180 days. The *Hatch-Waxman Act* involves the following patent listing requirements and processes:
   i. The innovator drug company must submit patent information with respect to its NDA listing patents that cover the approved product. FDA then lists this information in the *Orange Book* (*Approved Drug Products with Therapeutic Equivalence Evaluations*).[8]
   ii. A company intending to market a generic version of a listed drug (i.e., the ANDA holder) must certify to one of the following regarding the patents listed in connection with the innovator's NDA: (I) it has not been patented; (II) the applicable patent has expired; (III) the patent will expire on a given date and that the generic version will not be marketed before that date; or (IV) the listed patent is not infringed or invalid.

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iii. Certification under IV above (called paragraph IV certification) is the most misunderstood of the four and typically results in patent litigation. The generic company is required to notify the innovator about the ANDA filing and explain the reasons why it believes the generic version will not infringe the listed patent or why the listed patent is invalid. Upon notification, the innovator company has 45 days to file an infringement suit; the act permits such action by the patentee by treating the filing of a generic drug application as a hypothetical act of infringement such that patent issues may be determined before commercial sale of the product. If such a suit is filed, FDA withholds the approval of ANDA for up to 30 months while the case is decided. The 30-month period may be extended to a total of seven and a half years from approval if an ANDA with a paragraph IV certification is filed between year four and five after approval and the court takes longer than 30 months to decide the case.

1. Because of the potential of an untoward outcome, the existence of an ongoing paragraph IV challenge to a branded product by a generic house may result in the abandonment of a potential risk-based transaction if the parties are unable to agree on contractual protection.
2. Note: seven years of exclusivity is available for orphan drugs through a prohibition of approval of a generic drug application for the same indication under the *Orphan Drug Act*.

At a minimum, US-based NCEs that have undergone regulatory review (e.g., approval to treat patients in a safe and efficacious manner based upon clinical trial data), but do not have patent protection, are able to obtain a period of protection of up to five years via regulatory exclusivity as an incentive to develop the product. As described above, products successfully studied in pediatric patients in the US are entitled to an additional six months of market protection through regulatory exclusivity.[9,10] Therefore, some products may have no US patent protection but may still remain protected for up to five and a half additional years due to regulatory exclusivity alone. Unfortunately, this is typically insufficient to justify the extensive investment required to bring a new drug to market.

EU Patent Term

The patent term of pharmaceuticals in the EU may be extended by a supplementary protection certificate (SPC).[11] SPCs were introduced in 1992 to compensate originator companies for the time and cost of developing NCEs. A brief overview of the SPC process is provided below:

- Submitted within six months of the date of approval of the marketing authorization, the SPC is granted by the patent office in each Member State if the product is covered by a basic patent. Only one SPC is granted for each product (defined as the active ingredient(s) of a medicinal product) in each Member State.
- The SPC can be granted for a maximum period of five years, resulting in a maximum effective patent life of 15 years. The period of validity of an SPC is equal to the time elapsed between the date on which the application for a basic patent was first filed and the date of approval of the first marketing authorization in the European Economic Area (i.e., 27 countries of the EU, Liechtenstein, Norway and Iceland), reduced by five years.

EU marketing authorizations provide an eight-year period of data protection (to protect originator data from being accessed or used for another's marketing application) and a 10-year period of marketing protection (to reward the originator) for new pharmaceutical drugs.[12]

These periods commence from the date of the first marketing authorization granted in the Community. They are also harmonized, meaning that they apply equally to products submitted under the Centralised Procedure, Mutual Recognition Procedure or Decentralised Procedure.

The 10-year marketing protection period shall be extended to a maximum of 11 years (e.g., 10 + 1 year formula) if, during the first eight of those 10 years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. The regulation also provides incentives for studies in pediatric patients, including a six-month extension of the SPC for products covered by such a certificate and approved under a Marketing Authorization Application (MAA). To encourage pediatric studies for orphan indications, the regulation provides for a total of 12 years of marketing exclusivity rather than the 10 years provided for orphan indications in adults.

Summary

- The intellectual property assessment is the linchpin of the entire due diligence process.
- IP protection includes both the formal IP assessment as well as the regulatory exclusivity assessment. Together they form the basis of protection for a product from competition.
- The US *Drug Price Competition and Patent Term Restoration Act* of 1984, provides a pathway to standardize generic drug procedures.
- When IP vulnerability is discovered, it is often possible to diminish or even eliminate a risk through contractual language.

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10. *Guidance for Industry, Qualifying for Pediatric Exclusivity under Section 505(A) if the Federal Food, Drug, and Cosmetic Act. 30* June 1998.)
    a. Section 505(A) of *The Food and Drug Administration Modernization Act* required FDA to develop, prioritize, and publish a list of approved drugs for which additional pediatric information may produce health benefits in the pediatric populations and update it annually. As an incentive to industry to conduct studies requested by the Agency, Section 505(A) provides for a 6-month period of marketing exclusivity (pediatric exclusivity).
11. See EU regulation provided in Regulation (EC) No. 469/2009 (IDRAC 92690).
12. See EU regulation provided in Directive 2001/83/EC (IDRAC 37421) and Regulation 726/2004/EC (DRAC 44203).

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