

30-SECOND SUMMARY

Orphan drugs present unique risks – the potential return on investment is inherently constrained by small patient populations and attendant reimbursement challenges. Recognizing these challenges, some countries have passed laws designed to make the economic model associated with developing treatments for orphan diseases more attractive. The most meaningful incentive provided by the various orphan drug statutes is the period of market exclusivity available for qualifying drugs; however, there are still limitations. A comprehensive patent strategy provides a key complement to orphan exclusivity by buffering against the exceptions to orphan protection and extending the period of exclusivity to a point that better ensures a sufficient return on investment.



Adopt IP Protections to Ensure Regulatory Exclusivity for Orphan Drugs

By Randall Morin, Kerry Flynn, Fangli Chen and Eric Marandett

In-house counsel at biotech and pharmaceutical companies routinely confront the critical challenge of developing an IP strategy for drugs in development in a way that complements and enhances the regulatory strategy. The goal is to ensure sufficient exclusivity to maximize the return on the investment required to bring a drug to market. This complex balance is particularly difficult in the context of orphan drugs, where the market upon approval typically is relatively small, thus putting unavoidable constraints on the potential returns. In this context, providing some certainty around exclusivity is essential. This requires careful focus on the regulatory options, including obtaining and sustaining exclusivity afforded by the orphan drug statutes in place in certain jurisdictions, and on obtaining maximum patent protection. Strong patents can drive valuation, particularly where there is some uncertainty around the maintenance and/or scope of orphan protection.

This article provides an overview of the intellectual property and regulatory frameworks for orphan drugs in the United States and certain other developed and emerging markets. In particular, it looks at how to use patent protection as a complement to regulatory exclusivity in the orphan drug context. For example, the unfortunate experience of KV Pharmaceuticals with its orphan product Makena illustrates some of the limitations of orphan protection. In that case, orphan protection was successfully circumvented by a compounding pharmacy that did not have to seek FDA approval for its version of KV's drug and, therefore, was not subject to FDA enforcement of KV's orphan exclusivity. An effective patent strategy can help mitigate some of those limitations.

Rare diseases and orphan drug legislation

Generally speaking, diseases that affect a small percentage of the world population are considered rare diseases or orphan diseases. The United States Congress defines a "rare disease or condition" as one that affects less than 200,000 people in the United

States, or one that "affects more than 200,000 in the [United States] and for which there is no reasonable expectation that the cost of developing and making available in the [United States] a drug for such disease or condition will be recovered from sales in the [United States] of such drug." This definition explicitly acknowledges the economic dilemma associated with the huge investment required to develop treatment for a relatively small class of patients where, without sufficient exclusivity, the prospective return on investment may not justify the upfront research and development (R&D) costs.

Today, there are over 5,000 known rare diseases, 80 percent of which have been identified as genetic in nature, with incidence of less than one in 2,000 people. Symptoms of some rare diseases may appear at birth, or develop later in childhood or even during adult life. Other rare diseases are the result of infections (bacterial or viral), allergies, or are caused by degenerative and proliferative conditions. Currently, the number of rare diseases for which no treatment is available is estimated to be between 4,000 and 5,000 worldwide.

Regulatory exclusivity and patent protection each provide critical incentives for drug development by providing appropriate mechanisms to keep generic competition off the market for a period of time sufficient to justify the expense and risk associated with drug development. The orphan context presents unique risks where the potential return on investment is inherently constrained by small patient populations and attendant reimbursement challenges. Recognizing these challenges, certain countries have passed laws to provide additional incentives to encourage development of treatments for orphan diseases. In the United States, Congress passed the Orphan Drug Act in 1983 to foster the development and commercialization of drugs to treat rare diseases.

The Orphan Drug Act includes a number of incentives designed to make the economic model associated with developing treatments for orphan indications more attractive. Most significantly, the Act provides for seven-year market exclusivity following the market approval of an orphan drug — in contrast, a traditional drug that is a new chemical entity (i.e., not previously approved for any indication) receives only five years of data exclusivity. In addition, the Act provides for various tax credits, grants for drug development, fast-track approvals and expanded access to the Investigational New Drug Program.

A number of other countries have enacted statutes designed to provide similar incentives. For example, in 1993, Japan introduced the Orphan Drug Amendment to the Pharmaceutical Affairs Law. It establishes three criteria for orphan designation: 1) the number of patients affected must be less than 50,000 within the Japanese territories; 2) there must be a medical need with no suitable alternatives, or the efficacy and safety of the drug to be designated must be better than available drugs or interventions; and 3) there must be a high potential for actual development (i.e., the existence of a theoretical basis for the use of the drug and a feasible development plan). The incentives provided by the Japanese orphan designation include extension of the reexamination period (i.e., the period before a generic drug can enter the market) from the normal five-year period to a 10-year period for orphan drugs and a seven-year period for orphan devices. It also provides reduced fees, grants for orphan products development, fast-track review and tax credits.

Europe enacted its Orphan Drug Regulation in 2000. The European statute designates as "orphan" a disease or disorder that affects fewer than five in 10,000 citizens. It establishes a period for market exclusivity of 10



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Highlights from *KV Pharmaceutical Co. v. FDA*

- First significant challenge to an FDA decision on orphan drug exclusivity;
- FDA declined to enforce exclusivity for KV's drug, Makena;
- US District Court refused to issue an injunction compelling FDA to take action against infringers;
- Without patent protection, orphan drug exclusivity was KV's only means of protection for Makena; and
- KV Pharmaceuticals eventually filed for Chapter 11 bankruptcy.

years from authorization of an orphan drug product. A member state may not accept another application for marketing authorization or grant a marketing authorization for the same therapeutic indication for a similar medicinal product during that exclusivity period. The exclusivity, however, may be forfeited by the first applicant if the first applicant consents to a second application from another applicant; if the first applicant is unable to meet demand; if a similar product is found to be clinically superior; if, at the end of the first five years, a Member State shows that the product is sufficiently profitable not to justify maintaining its market exclusivity; and/or if the statutory criteria are otherwise no longer met.

Many other countries have introduced comparable legislation. For example, Singapore adopted orphan drug legislation in 1991, Australia in 1998, Taiwan in 2000, and South Korea in 2007. Most recently, in October 2012, Canada announced that it will introduce a regulatory framework for authorization of orphan drugs. Jurisdictions with orphan drug regulations offer various incentives, including market exclusivity, tax credits, regulatory fee waivers and fast-track approval for orphan drugs. The particular incentives available vary from jurisdiction to jurisdiction.

Orphan exclusivity compared to data exclusivity

The most meaningful incentive provided by the various orphan drug statutes is the period of market exclusivity available for qualifying drugs. This

orphan exclusivity will be granted only to the first sponsor who obtains marketing approval for a designated drug or biological product for the orphan indication. The US Orphan Drug Act of 1983 can be used as an example to illustrate how it works. The seven-year market exclusivity period provided by the Orphan Drug Act is granted only to the first sponsor who obtains marketing approval for a designated orphan drug. The exclusivity begins on the date that the drug receives Food and Drug Administration approval, and applies only to the orphan indication for which the drug has been designated and approved.

During the seven-year orphan exclusivity period, the FDA cannot approve an application using the same drug for the same orphan indication. It does not, however, preclude approval of either a drug using a different active moiety for the same indication, or the same drug for a different indication. The statute permits approval of a "clinically superior" product that uses the "same active moiety." In other words, if a competitor wishes to introduce a drug using the same active moiety for the same indication, the burden is on the competitor to prove that its drug is therapeutically superior when compared to the first drug approved for the same orphan indication. Thus, orphan exclusivity provides a meaningful period of protection from competition.

Orphan exclusivity differs from the data exclusivity provided by Hatch-Waxman Act and the more recently enacted biosimilar statute.¹ The

Hatch-Waxman Act provides five years of data exclusivity for new chemical entities (NCEs) not previously approved by the FDA. For biosimilars, an application for a biosimilar license may not be filed for four years after approval of the reference Biologics License Application ("BLA"), and its approval may not be made effective until 12 years after the BLA license. However, the data exclusivity provided by the Hatch-Waxman Act and the biosimilar statute merely prevents competitors from using an Abbreviated New Drug Application (ANDA) or biosimilar application, respectively, and does not prevent a competitor who runs its own clinical trials from marketing its competing drug product. In contrast, orphan exclusivity bars entry even from a competitor filing its own New Drug Application or BLA supported by its own clinical trials, so long as the competitor is seeking approval of the same drug for the same orphan indication, and other conditions are met (i.e., the competitor does not show clinical superiority). In this respect, orphan exclusivity is broader than data exclusivity. The scope of orphan exclusivity thus can be viewed in certain respects as analogous to the protection provided by a valid and infringed method of use patent covering the use of a particular drug substance (narrowly defined to exclude superior formulations) to treat the orphan indication, with a built-in injunction enforced by the FDA.

Interplay of patent and regulatory exclusivity

In the orphan context, in-house counsel at biotech and pharmaceutical companies routinely confront the question of how best to develop a patent strategy to enhance regulatory exclusivity for orphan drugs. Several factors must be taken into consideration.

- *How can patent protection be used to expand the scope of protection beyond the particular indication covered by the orphan exclusivity?*

Orphan drug exclusivity does not extend to other uses for the same drug, but a valid and enforceable patent can. In this way, patent protection helps address the competitive risk associated with off-label use.

For example, as discussed above, during the seven-year period of orphan exclusivity, the FDA cannot approve the same drug for the same orphan indication, but can approve the same drug for another disease or condition. However, once a drug is approved for sale, physicians may prescribe the drug “off-label” for disorders other than the specific conditions for which the products are approved. Orphan drug exclusivity does not extend to other uses for the same drug, but a valid and enforceable patent can. In this way, patent protection helps address the competitive risk associated with off-label use. For example, a sponsor of an orphan drug can seek patent protection for the drug substance itself, for various therapeutic uses of the drug substance, including, but not limited to, the relevant orphan

indication, and for various processes of making the drug substance, assuming such aspects are novel, useful and nonobvious in accordance with patent law. Such patents can effectively foreclose competition with an orphan product through the back door of off-label use.

- *Can patent protection extend the actual market exclusivity for a drug, thereby enhancing the incentive for investment?* For a typical drug, market exclusivity of 11 to 13 years may be necessary to secure sufficient incentives for the expensive and risky investment in drug development. In view of the small market for an orphan drug and the need to maintain sufficiently high prices to recoup the upfront R&D investment, obtaining an adequate period of market exclusivity is critical to justify the equally expensive and complex investment in orphan drug development. Thus, patents can play an important role in extending the actual market exclusivity period to create the necessary incentive for investment.
- *What is an effective patent strategy?* To seek patent protection, an invention must be new, useful and nonobvious. An applicant for patent must also provide written description of the invention and enable a person skilled in the art

to make and use it. As for any other drugs, patent claims that most effectively secure exclusivity for orphan drugs are those that cover the drug substance as a new composition of matter. But the discovery of a new compound typically occurs at an early stage in the course of drug development, long before therapeutic value is validated in clinical trials. This is especially true for orphan indications, because the therapeutic efficacy in an orphan indication sometimes is discovered later in the course of study, and it can take longer to complete clinical trials due to the small patient populations.

Generally, it takes an average of about 10 years to bring a regular drug candidate to market. For orphan drugs, it can take even longer. Patent law, on the other hand, promotes early filing. By the time an orphan drug gets to market, some early-filed patents may have little remaining life. Although some of the lost time during clinical trials and regulatory review may be restored through patent term extension,² this time lag poses particular challenges for patent protection for orphan drugs, and requires more thoughtful and strategic patent filing and life cycle management.

The most important step in using patent protection to

| Orphan drug incentives at a glance | | | | | |
|------------------------------------|-------------------------------|---|---------------------------|---------------------|-------------|
| | Market exclusivity | Fast-track approval | Tax credits | Protocol assistance | Fee waivers |
| Australia | 5 years (as with other drugs) | Yes | No | Yes | Yes |
| European Union | 10 years | Yes | Varies by EU member state | Yes | Yes |
| Japan | 10 years | Yes | Yes | Yes | Yes |
| Singapore | None | Orphan drugs given priority in registration | No | No | No |
| South Korea | 6 years | No | No | No | No |
| Taiwan | 10 years | Yes | No | Yes | No |
| United States | 7 years | Yes | Yes | Yes | Yes |

The most important step in using patent protection to supplement orphan exclusivity is to patent the drug product composition of matter. However, because of the long development timelines associated with orphan development, maximizing exclusivity often will require additional filings covering advances made during the development process.

supplement orphan exclusivity is to patent the drug product composition of matter. However, because of the long development timelines associated with orphan development, maximizing exclusivity often will require additional filings covering advances made during the development process. Such subsequent patent filings can be directed to dosage forms, formulations, administration mode, drug metabolites, a particular polymorph, a single enantiomer isolated from a racemic mixture, or combination therapy.

Prior art, sometimes created by the drug developer's own earlier filings, can present a significant obstacle to subsequent patent filings. Therefore, to develop an effective patent portfolio to maximize exclusivity, companies need to strategically plan each filing. For example, to leave room for subsequent patent filings, companies should avoid disclosing, explicitly or inherently, the therapeutic uses, dosages and formulations in the earlier new compound composition filings, in order to avoid generating novelty-destroying prior art.

To address potential obviousness issues, a company may need to show why such new therapeutic use, dosages and formulations are not obvious to a person working in the field, coupled with unexpected properties provided by such new therapeutic use, dosages and formulations.

- *Has your company struck the right balance between patent rights and orphan exclusivity rights in order to protect your drug around the world?* Companies have greater control and flexibility in enforcing patent rights as compared with orphan exclusivity rights. The FDA (or its regulatory counterparts in other countries) primarily enforces orphan exclusivity, without the need for drug sponsors to bring costly and risky infringement actions. This may be particularly advantageous in countries that do not have well established and functioning patent enforcement systems, or in situations in which patent protection is not an option. On the other hand, a company itself controls when and how to assert its patents, without needing to rely on action by an outside authority like the FDA. The recent *KV v. FDA* case (discussed below) illustrates the risk associated with relying on government action to maintain exclusivity.

The limitations of orphan exclusivity

The recent lawsuit brought by KV Pharmaceuticals Company (KV) against the FDA over its orphan drug product Makena provides a stark example of the potential shortcomings of orphan protection. KV and its wholly owned subsidiary Ther-RX Corporation (Ther-RX) own and market a drug called Makena, which is a hydroxyprogesterone caproate injection (also known as "17P"). On Jan. 25, 2007, the FDA designated Makena as an "orphan

Patent protection complements orphan exclusivity

- It protects against gaps in orphan protection;
- Extends exclusivity to adequately incentivize the investment; and
- Offers more robust enforcement rights.

drug" to be used for the prevention of preterm birth in women who have a singleton pregnancy and a history of prior preterm delivery. Makena was approved on Feb. 3, 2011, thereby commencing its seven-year orphan exclusivity period. However, for a number of years before the FDA approved Makena, women were treated for risk of preterm birth with versions of hydroxyprogesterone caproate that were compounded by entities known as "compounding pharmacies" or "compounders." When Makena was released, there was some controversy over its high listed price. In a surprising move, the FDA issued a statement in March 2011 stating, in relevant part, that "[i]n order to support access to this important drug, at this time and under this unique situation, the FDA does not intend to take enforcement action against pharmacies that compound hydroxyprogesterone caproate based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards for compounding sterile products." The FDA issued further public statements on Makena on Nov. 8, 2011 and June 15, 2012, and none of these statements have announced an intent to take enforcement action against compounded 17P.

ACC EXTRAS ON... Intellectual property

ACC Docket

Critical Components in IP Licensing (Sep. 2011). www.acc.com/docket/ip-lic_sep11

InfoPAKSM

Intellectual Property Primer – Patents, Trademarks, Copyrights, and Trade Secrets – An Introduction to Intellectual Property for In-House Counsel in a Global Dimension, 4th Edition (Sep. 2012). www.acc.com/infopaks/ipprimer_sep12

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Presentation

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On July 5, 2012, KV sued the FDA. In its complaint, KV asserted that “FDA’s statement and inaction have undermined the exclusivity conferred with the orphan drug designation and devalued their substantial investment in the drug.” The complaint asked the court to issue an injunction that would proactively require the FDA to enforce Makena’s orphan designation by taking action against the compounders. The judge dismissed the lawsuit, citing the Supreme Court directive that “an agency’s decision not to prosecute or enforce, whether through civil or criminal process, is a decision generally committed to an agency’s absolute discretion” and is therefore presumed to be unreviewable by the court. Moreover, it is uncertain whether the FDA would have had the authority to take action against the compounders. Drug products made by compounders typically are not subject to the FDA approval process and, instead, are regulated by the states. Congress presently is considering proposed legislation that, if enacted, would expand FDA authority over compounders.

KV’s business model was built on the presumption that sales of Makena would be sufficient to at least recoup its substantial investment in development of the product. The compounded version of 17P displaced Makena in the market and substantially undercut

its sales. It does not appear that KV obtained sufficient patent protection for Makena. Indeed, no infringement action has been brought against the compounding pharmacies. KV Pharmaceuticals eventually filed a voluntary Chapter 11 petition in the US Bankruptcy Court.

The facts and circumstances surrounding the Makena litigation were quite unique. Nevertheless, the case illustrates the vulnerability of orphan exclusivity protection and how little control a drug sponsor may have over enforcing the exclusivity for its product. By contrast, despite the costs and uncertainty associated with patent litigation, the patent system does provide a robust avenue for enforcing patent rights. Indeed, patent protection historically has been a critical value driver necessary to encourage the extraordinary expense and risk of drug development, even for drugs that serve large patient populations and, therefore, carry the potential for substantial economic reward even over a short period of exclusivity.

For orphan products with small and sometimes diffuse patient populations, the risk is particularly acute. The development costs are just as substantial, the development timeline often is longer, and the development risks associated with treating a smaller patient population often are greater. The somewhat

longer (seven-year) and more robust regulatory protection alone often is not enough to justify the expense. A comprehensive patent strategy provides a key complement to orphan exclusivity by providing a buffer against the exceptions to orphan protection (e.g., the enforcement problem encountered in the Makena situation).

An IP strategy that is closely coordinated with clinical development is key to success. As explained above, companies should rigorously seek protection for novel compounds, formulations, manufacturing processes and any other innovations discovered as the development process progresses, to ensure maximum protection for the resulting orphan treatment and to supplement the exclusivity provided by orphan drug statutes. The best way to ensure sufficient return on the investment in orphan drug development is to combine the benefits of regulatory exclusivity and patent protection. **ACC**

NOTES

1. In March of 2010, Congress enacted the Biologics Price Competition and Innovation Act of 2009 (BCPI Act), as part of the Patient Protection and Affordable Care Act. The BCPI Act creates a period of data exclusivity after initial FDA approval of a biological product, during which applications for biosimilar products may not be based on the original applicant’s data.
2. See 35 U.S.C. 156: A patent on an FDA-approved drug may be entitled to a term extension of up to five years for some of the time lost during clinical trials and regulatory review. The remaining patent life after extension may not exceed 14 years beyond the date of FDA approval.