

Reflections On The Remarkable Rise Of Orphan Drugs

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The Orphan Drug Act[1] was signed into law by President Ronald Reagan in January 1983. Prior to the ODA's passage, drugs specifically targeting rare diseases were generally not developed. The primary cause of this deficit was economic. Because of the smaller market size associated with rare diseases, pharmaceutical companies could not recoup the significant research and development costs for these drugs. Recognizing the significant unmet medical need, Congress crafted the ODA to provide regulatory and financial incentives for pharmaceutical companies to develop drugs targeting these rare diseases. Such drugs are termed orphan drugs.[2] The ODA, in encouraging the development of drugs to treat small patient populations, is an example of the application of democratic principles in pharmaceutical legislation.

The ODA initially received a cool reception. Two of the ODA's provisions were suboptimal from a drug innovator viewpoint. First, the ODA's award of seven years of market exclusivity to orphan drug companies who obtained an orphan drug approval only applied to drugs that could not be patented. Second, the U.S. Food and Drug Administration would only provide an orphan drug designation when there was no reasonable expectation that development costs would be recovered by U.S. drug sales. Few pharmaceutical companies were willing to provide such financial disclosures.

Recognizing that the ODA was deficient, Congress engaged in legislative fine-tuning. In 1984, the ODA was amended to classify a rare disease as one: (i) affecting fewer than 200,000 persons in the U.S. or (ii) for which there is no reasonable expectation of recovering development costs through U.S. sales.[3] Under the expanded definition, pharmaceutical companies demonstrating the fewer-than-200,000-persons requirement could avoid the burdensome financial disclosure alternative.

In 1985, the ODA was further amended to extend the award of seven years of marketing exclusivity to both patented and nonpatented drugs.[4][5] Additionally, in 1997, the Food and Drug Administration Modernization Act exempted designated orphan drug candidates from user fee legislation.[6] The FDAMA also allowed, on an annualized case-by-case basis, sponsors of approved orphan drugs to seek waivers of annual postapproval establishment and product fees. From the ODA's inception in 1983, 484 orphan drugs have been approved by the FDA.[7] In 2014 alone, 47 orphan drug approvals were granted



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by the FDA.[8][9] It is predicted that orphan drug sales in the U.S. will account for 19 percent of total prescription drug sales (approximately \$176 billion) by 2020,[10] and will grow at an annual rate of nearly 11 percent through 2020. The projected orphan drug sales growth rate is more than double the percentage annual growth rate predicted for drugs targeting larger patient populations.[11] Depending on the estimating entity, there are 5,000 to 8,000 rare diseases (i.e., potential orphan drug target diseases), out of which only about 10 percent have treatments.[12] In 2014, the average orphan drug cost per patient per year was U.S. \$137,782, compared to an average per patient per year cost of U.S. \$20,875 for a nonorphan drug.[13] Orphan drugs are so compelling that large pharmaceutical companies are now significant players in the space. Indeed, one report estimates that Bristol-Myers Squibb Co. will be the top orphan drug seller by 2020.[14] The orphan drug is clearly on the rise.[15]

Advantages and Acquisition Diligence Issues

The ODA, current marketplace conditions and the large number of unmet rare disease medical needs, provide unique incentives that are important drivers of orphan drug growth. These advantages also raise specific diligence questions when an acquirer is considering the purchase of an orphan drug or candidate and its associated intellectual property.

First, a drug sponsor is required to apply for orphan designation prior to submitting a new drug application to market a drug for orphan indication.[16] Thus, recommended diligence practices are to ensure that a complete orphan designation request has been timely submitted and to confirm that the FDA's orphan designation has been granted.

Next, the ODA provides for a tax credit of up to 50 percent of qualified clinical research expenses incurred in developing the orphan drug candidate. The tax credit need not be exhausted for the year of grant and may be transferred to the acquirer. Recommended diligence practices therefore include confirming tax credit eligibility, determining if a tax credit was issued and, if issued, what balance of the tax credit remains and may be transferrable.

Orphan drug designation must remain intact. For example, orphan exclusivity can be suspended or withdrawn if the orphan designation is revoked. Revocation of orphan designation can occur if the orphan drug designation request: (i) contained an untrue statement of material fact; (ii) omitted required material information; or (iii) if the drug was not eligible for orphan designation at the time of the orphan designation request.[17] Market exclusivity can also be lost (e.g., the FDA can approve a NDA for the same drug and orphan indication) if the sponsor cannot assure sufficient approved orphan drug availability.[18] Recommended diligence practices therefore include confirming orphan designation eligibility at the time of designation request, obtaining representations and warranties that the orphan drug designation request contained no untrue statement of material fact and omitted no required material information and confirming drug supply chain robustness and sufficient orphan drug availability.

Orphan drugs are also eligible for FDA clinical study grants.[19] These grants have limited renewability and can generally increase in amount as the drug progresses from phase I to phases II through III. Other types of grants from government agencies and private foundations may also have been awarded (e.g., to fund research leading to patents). Grants may affect tax breaks, come with royalty obligations and impose manufacturing covenants on the orphan drug sponsor. Accordingly, a recommended diligence practice is to determine if grants were awarded and if these grants carry constraints or conditions that could materially affect the orphan drug sponsor and its acquirer.

Orphan drugs may also be eligible for approval accelerating tools (e.g., breakthrough designation accelerated approval). Thus, a recommended diligence practice is to make sure all eligible advantages are utilized in the FDA approval process.

Orphan market exclusivity, because it is limited to the approved indication, has a value that is in part determined by the orphan drug's competitive environment. For example, if the same drug, in the same dose and dosage form is available generically, the competing generic may be prescribed and substituted off-label for the drug that has obtained orphan approval. This substitution would likely significantly decrease the orphan drug's market share.

Also, if a competing drug has been approved for the same orphan indication, and both drugs have about the same performance features, formularies may play one orphan drug manufacturer against another, ultimately listing only one of the approved orphan drugs. The unlisted orphan drug would lose market share in proportion to the number of patients served (constrained) by the formulary.[20] On the other hand, if the orphan drug is the only drug that has only been approved for a specific indication, and exclusivities and/or patent protection are in force, these conditions are favorable for market share optimization. Accordingly, recommended diligence practices include familiarization with current and predicted product landscape, and factoring this knowledge into projected orphan drug valuation.

Finally, governmental interpretation of federal statutory law regarding pharmaceutical prices may also impact future orphan drug profitability. Thus, a recommended diligence practice is to closely follow and remain abreast of legal developments in this space.[21]

Conclusion

Orphan drugs are increasingly important to pharmaceutical companies and patients with rare diseases. The ODA's incentives, potentially strong marketplace rewards and large unmet medical needs are all important drivers of orphan drug growth. The unique niche of orphan drugs raises orphan drug specific diligence questions for companies considering acquiring an orphan drug or drug candidate and its underlying associated intellectual property. General diligence protocols should be appropriately tailored for orphan drugs and drug candidates.

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[1] Public Law 97-414 (1983).

[2] Although a regulatory exclusivity is not, per se, a financial incentive, orphan drug approved-indication seven-year market exclusivity provides a market environment that can significantly contribute to pharmaceutical company profits. Thus, orphan regulatory exclusivity can translate into a significant financial incentive.

[3] See Public Law No. 98-551 (1984).

[4] Proponents have argued that regulatory (e.g., data and market) exclusivities can serve as an alternative to patent protection. Orphan drug history undercuts this argument. Orphan drug approval did not take off until the law was changed allowing patented molecules to become orphan drugs. Further, venture capitalists generally will not invest in technologies that cannot be patented. Without patent protection, many orphan drugs would never have been researched and developed because their sponsors would not have been funded. Thus, the history of orphan drugs indicates that both patents and regulatory exclusivities are necessary to promote optimal new drug development.

[5] See Public Law No. 99-91 (1985).

[6] New drug application fees paid by drug companies under the Prescription Drug User Fee Act are steep. For example, in 2014, the standard PDUFA fee for a NDA with clinical data was approximately \$2.17 million. Thus, the ODA's exemption from paying PDUFA fees is a significant financial incentive.

[7] See Search Orphan Drug Designations and Approvals, FDA, available electronically at: <http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm>, last accessed Jan. 20, 2015.

[8] Id.

[9] Not all approvals were new chemical entities.

[10] C. Helfand, Report: Orphan drugs to nab 19 percent of drug sales by 2020 — if payers don't balk, that is, FiercePharma, November 3, 2014, available electronically at: <http://www.fiercepharma.com/story/report-orphan-drugs-nab-19-drug-sales-2020-if-payers-dont-balk/2014-11-03>, last accessed Jan. 20, 2014.

[11] Id.

[12] S. Kumari et al., Trends in Development of Orphan Drugs — A Review, Open Access Scientific Reports, Oct. 8, 2013.

[13] D. Vaczek, Orphan Drugs a Niche no Longer, Medical Marketing & Media, Oct. 30, 2014, available electronically at: <http://www.mmm-online.com/orphan-drugs-a-niche-no-longer/article/380333/>, last accessed Jan. 20, 2014.

[14] C. Helfand, Report: Orphan drugs to nab 19 percent of drug sales by 2020 — if payers don't balk, that is, FiercePharma, Nov. 3, 2014, available electronically at: <http://www.fiercepharma.com/story/report-orphan-drugs-nab-19-drug-sales-2020-if-payers-dont-balk/2014-11-03>, last accessed Jan. 20, 2014.

[15] Orphan drug approvals also reached a new high in Europe in 2014, with 17 approvals. See M. Mezher, Orphan Drugs in the EU: A Record Breaking Year, RAPS, Jan. 13, 2015, available electronically at: <http://www.raps.org/Regulatory-Focus/News/2015/01/13/21063/Orphan-Drugs-in-the-EU-A-Record-Breaking-Year/>, last accessed Jan. 20, 2015.

[16] See Public Law No. 100-290 (1988).

[17] See 21 C.F.R. § 316.29.

[18] In some instances, a second drug legally considered to be the “same” drug, for the same therapeutic use as an approved orphan drug, can demonstrate clinical superiority. When this occurs, the “same” drug would then be legally classified as a “different” drug and, when the FDA approved, would not be blocked by the earlier approved orphan drug’s exclusivity. See 56 Fed. Reg. 3338 (1991).

[19] FDA funds orphan drug clinical grants at around 15 percent of requests per year based on competitive priority review ranking scores. FDA grants can run from \$200,000 per year for dose ranging trials to \$400,000 per year for phase II and III trials.

[20] Playing drug manufacturers against each other is not confined to orphan drugs. In late 2014, pharmacy benefit manager Express Scripts Holding Co. and drug maker AbbVie Inc. entered into a multiyear agreement in which AbbVie agreed to a major discount for its Viekira Pak (ombitasvir, paritaprevir, ritonavir and dasabuvir) hepatitis C treatment in return for Express Scripts exclusively offering the new treatment combination to its members with relaxed prescriber submission and patient reimbursement requirements. The agreement effectively eliminates rival Gilead Sciences Inc.’s hepatitis C treatments from Express Scripts’ formulary. See R. Hernandez, Express Scripts and AbbVie Ink Landmark Formulary Exclusivity Deal, BioPharm International.com, Dec. 22, 2014, available electronically at: <http://www.biopharminternational.com/express-scripts-and-abbvie-ink-landmark-formulary-exclusivity-deal>, last accessed Jan. 20, 2015.

[21] See, e.g., 42 U.S.C. § 256(b). See also, e.g., M.S. Leonard, Pharma Industry Group Sues U.S. Again Over Orphan Drug Rules, Nov. 11, 2014.