CHAPTER NINETEEN

From "Recycled Molecule" to Orphan Drug

Lessons from Makena

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I. INTRODUCTION

In the nearly thirty years since the Orphan Drug Act was passed, its package of user fee exemptions, grants and tax credits for clinical trial costs, and exclusive marketing rights has been controversial. The spotlight on orphan drugs has intensified in recent years as the number of orphan drugs that cost hundreds of thousands of dollars a year and bring in hundreds of millions of dollars in revenue continues to grow. Disputes have arisen over the Orphan Drug Act's application to so-called "recycled molecules"—older drugs that may have already been available to patients in compounded or generic form before they were designated "orphan drugs" and approved for marketing as such. Perhaps the most high profile of these is Makena, a branded version of the synthetic hormone 17-alpha hydroxyprogesterone caproate (17P), which the U.S. Food and Drug Administration (FDA) approved in February 2011 to treat pregnant women at high risk of giving birth prematurely. Makena was doubly controversial because, in addition to involving a recycled molecule that was already available to

patients from compounding pharmacies, the drug's sponsor relied on government-funded research to secure FDA's approval.

After FDA approved Makena, its manufacturer, K-V Pharmaceutical, set the price of the drug at $1,440 per injection, for a cost per pregnancy of approximately $30,000; the cost of the compounded version was $15 per injection, for a cost per pregnancy of approximately $300 (Patel and Rumore 2012:406). Under pressure from advocacy groups, health care providers, Congress, and, reportedly, the White House, FDA took an unprecedented step, announcing that it would exercise its "enforcement discretion" and allow pharmacies to continue compounding 17P (FDA 2011). In so doing, the agency eased access to the drug but thwarted K-V's expectation of exclusivity, sparking since-settled litigation. FDA also reinvigorated a perennial debate about how to strike the balance between, on the one hand, incentivizing research and development of new orphan drugs and, on the other hand, ensuring that the drugs, once developed, are accessible to patients.

The balance struck by the Orphan Drug Act could be adjusted in favor of access in a number of ways, including shortening the exclusivity period, allowing for limited competition during the exclusivity period, and implementing a cap on drug prices. This chapter reviews these policy levers, focusing on the degree to which they address concerns about access, the adoption and implementation challenges they pose, and their potential for collateral effects. I also raise the alternative, suggested by the Makena case, of giving FDA the authority to decide whether to award market exclusivity on a case-by-case basis, taking into account factors such as the need to provide a reasonable reward for a company's investment, the degree to which the application for marketing approval relies on government research, the public health benefits of the drug at issue, and whether the drug is already available in compounded or generic form.

I conclude by recommending against amending the Orphan Drug Act to modify the exclusivity period or to allow FDA to take a case-by-case approach to awards of exclusivity. The first recommendation would not account for differences in value of different orphan drugs, while the second would come at a significant cost to the predictability of the regulatory process. Both would likely reduce the level of investment in orphan drug research and development. Potentially preferable are incremental reforms such as an amendment establishing a

formal mechanism through which patients or others could challenge as inadequate a company's patient assistance program or other efforts to ensure that individual patients who cannot afford a drug are nonetheless able to access it. Such a mechanism could have a number of advantages over the status quo, especially in cases in which the patient population lacks the political appeal and salience of expectant mothers. If the Orphan Drug Act is amended to allow access-based challenges, an agency or entity other than FDA, with its historic focus on safety and efficacy, should be charged with adjudicating the claims.

II. THE CURRENT APPROACH TO INCENTIVIZING AND SUPPORTING ORPHAN DRUG RESEARCH AND DEVELOPMENT IN THE UNITED STATES

The National Institutes of Health (NIH) has identified close to 7,000 rare diseases, defined as those that affect fewer than 200,000 people in the United States (NIH 2013). Altogether, such diseases affect 25 to 30 million—nearly one in ten—people within the United States (NIH 2013). For a number of reasons, including that a drug's potential profitability hinges in part on the size of the population affected by the disease the drug treats, these diseases were not historically the focus of the pharmaceutical industry's research and development pipeline.

When the Orphan Drug Act (Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified principally at 21 USC §§ 360aa–360ee)) was signed into law in 1983, only thirty-eight orphan drugs had been developed (Rare Diseases Orphan Product Development Act of 2002, Pub. L. No. 107-281, § 2, 116 Stat. 1992 (2002)). In the decade before the Act's passage, FDA had approved just ten orphan drugs (Murphy et. al. 2012:482). In the decade afterward, the agency approved over 220 new orphan drugs and there were another 800 being researched (Pub. L. No. 107-281, § 2). By the middle of 2014, FDA had issued 3,127 orphan drug designations and 458 orphan drug approvals (FDA 2014). There is broad agreement that the act has succeeded in incentivizing and supporting research into, and commercialization of, orphan drugs.

The Orphan Drug Act takes a multipronged approach to encouraging the private sector to develop treatments for rare diseases.

The Act provides for grants and a tax credit for sponsors of orphan drugs, and it exempts them from the user fees that would otherwise apply for investigational new drug and new drug applications (Murphy et al. 2012:481–82). Most important from the perspective of the pharmaceutical industry, the Act also provides for a seven-year period of market exclusivity, which takes effect when and if FDA approves a drug for sale to treat a rare disease (ibid., 482). Unlike the five-year-long grant of data exclusivity that is provided for in the Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as the Hatch-Waxman Act), the Orphan Drug Act's grant of exclusivity does not hinge on the drug being a new chemical entity. Congress was not only concerned about the failure to discover new treatments to treat orphan diseases; it was also concerned about the failure to bring such treatments to market once discovered (Kux 2011). The act was intentionally designed to incentivize manufacturers to make and sell "old" drugs for orphan uses (ibid.).

The Orphan Drug Act's grant of exclusivity is subject to a limited number of narrow exceptions. First, if a sponsor can show that the drug it has developed, while the same as a designated orphan drug, is nonetheless clinically superior, the second sponsor's drug can also be so designated (21 CFR § 316.20(a)). Second, the act permits FDA to approve additional applications "if . . . the Secretary finds, after providing the holder notice and opportunity for the submission of views, that in such period the holder of the approved application or of the license cannot assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated" (21 USC § 360cc(b)(2)). Finally, the statute provides that FDA can approve additional applications for permission to manufacture an orphan drug if the holder of the original license consents (21 USC § 360cc(b)(1)).

III. COST AND ACCESS CONCERNS ARISING OUT OF THE CURRENT APPROACH

In 2001, the Office of Inspector General (OIG) of the Department of Health and Human Services issued a report in which it concluded that the implementation of the Orphan Drug Act had not raised significant access concerns (OIG 2001:9). Drug shortages rarely occurred, and

although some orphan drugs were very costly, patients were nonetheless able to access them. The OIG noted that the very high prices of certain orphan drugs, and the very high profits reported by certain orphan drug manufacturers, had spurred Congress to consider amendments to the Act, but no such amendments were signed into law (ibid., 10).

In recent years, concerns about the price of orphan drugs have again come to the fore. In 2011, the "increasingly hot orphan drug market" was worth more than $50 billion and it was estimated to "turn . . . out blockbusters at the same rate as the broader industry" (Thomas 2013). In 2008, according to an analysis conducted by André Côté and Bernard Keating (2012:1186), there were forty-three drugs with at least one orphan designation that earned over $1 billion in revenue each year.

The price of an orphan drug is determined in the same way that the price of a non-orphan drug is. Among the factors companies may consider are (1) their own investment in researching and developing the drug, (2) the cost of manufacturing the drug, which can turn in part on the complexity of the molecule, (3) the cost of marketing and distributing the drug, (4) the medical benefit of the drug, (5) whether there are competing drugs and, if so, their price, (6) the prevalence of the disease or diseases the drug can be used to treat, and (7) relevant government regulation. Côté and Keating argue that these factors do not explain the high price of orphan drugs. They claim that the research and development costs of orphan drugs are significantly less than for standard drugs, in part because orphan drugs are often approved on the basis of fewer, smaller clinical trials. Marketing costs are reduced as well because "[p]atients with rare diseases are, for the most part, referred to and followed by teams of specialists, doctors, and pharmacists in tertiary hospitals[,]" and "[s]pecialists are exposed to the marketing of orphan drugs on a regular basis through their clinical activities, teaching activities, and research activities, and through their participation in international meetings" (ibid., 1189).

Côté and Keating (2012:1189) contend that in fact orphan drug "pricing is based on what patients and/or third-party payers are willing to pay." They explain that "[b]ecause orphan molecules are targeted at a captive market and have no therapeutic equivalents, third-party payer organizations have little room for maneuver and often resign themselves to accepting the manufacturer's suggested price, all the more so because they are subjected both to the influence of the media and to pressure from patient associations" (ibid.).

Eline Picavet and colleagues (2011:275) have taken Côté and Keating's argument a step further. Using data from Belgium from 2010, they analyzed "whether orphan drug designation status has an influence on the price setting of drugs for rare disease indications" (ibid.). To determine this, they compared the prices of designated orphan drugs to the prices of drugs that were used to treat rare diseases but were not so designated. They found that "[t]he median price per [dose] was higher for designated orphan drugs . . . than for non-designated drugs" (ibid., 277).

In many cases, individual patients are able to avoid paying an orphan drug's high price. In an article about the orphan drug Gattex, a treatment for short bowel syndrome marketed by NPS Pharmaceuticals, the *New York Times* reported that "[d]espite the high cost of the drug, NPS executives say few, if any, patients will have to pay much for it" (Thomas 2013). If a patient is privately insured, the company will cover his or her out-of-pocket expenses in excess of $10 a month. Foundations supported by the company will cover out-of-pocket expenses incurred by patients on Medicare and Medicaid. Finally, the company will provide patients who do not have insurance of any kind with Gattex free of charge. Payers are, of course, not provided with similar protections, and the pressure on them is increasing.

IV. THE CURRENT APPROACH DISRUPTED: THE CONVOLUTED REGULATORY HISTORY OF 17-ALPHA HYDROXYPROGESTERONE CAPROATE

Price and access concerns are perhaps most intense when orphan drug exclusivity is granted to "recycled molecules" such as 17-alpha hydroxyprogesterone caproate (17P), which was first approved in 1956 (Kim 2013:548). Marketed under the brand name Delalutin, 17P was used to treat various conditions at various times. In 2000, FDA withdrew its approval of Delalutin at the request of the drug's manufacturer, Bristol-Myers Squibb, which had not sold it for several years (ibid., 548–49).

In 2003, the *New England Journal of Medicine* published an article reporting on the results of a clinical trial of 17P funded by the National Institute of Child Health and Human Development (Meis

et al. 2003). The clinical trial showed that 17P was effective in preventing preterm labor and delivery in pregnant women with a documented history of a spontaneous premature birth. A follow-up study published in 2007 demonstrated that children exposed to 17P in the second and third semesters, which is when the drug is given to prevent prematurity, had no adverse health outcomes (Northen et al. 2007). The drug, which is administered via intramuscular injection, became the standard of care for pregnant women with a history of preterm birth, but because it was not commercially available in the wake of Delalutin's withdrawal, prescriptions for it had to be filled at compounding pharmacies (Patel and Rumore 2012:405).

Not surprisingly, interest arose in commercializing 17P. On May 4, 2006, a new drug application was filed seeking approval to market it for the prevention of recurrent premature birth (Adeza Biomedical Corporation 2006). The drug received orphan drug designation on January 25, 2007, and was finally approved for marketing, under the name Makena, on February 3, 2011 (FDA 2014).

Also on February 3, 2011, FDA denied an October 24, 2007 Citizen Petition from the Sidelines National Support Network seeking revocation of Makena's orphan-drug designation. Sidelines argued that orphan drug designation was inappropriate because, among other reasons, (1) should the drug "be approved it would have achieved that status and the attainment of a seven-year monopoly . . . via utilization, not of its own original research, but of data licensed from a *government-funded* clinical trial" and (2) "if marketing exclusivity is assigned to [the] product, all chance of competitive pricing will be lost for the exclusivity period" (Sidelines 2007).

In its response, FDA emphasized that although it administers the orphan drug designation and approval process, its discretion is very limited (Kux 2011). Under current law, if a drug is being developed to treat a "rare disease or condition," FDA must grant a request from the sponsor that the drug be designated an orphan drug; if an orphan drug is subsequently approved for marketing, orphan-drug exclusivity occurs automatically. FDA cannot revoke a drug's designation unless "(1) [t]he request for designation contained an untrue statement of material fact; or (2) [t]he request for designation omitted material information required by this part; or (3) FDA subsequently finds that the drug in fact had not been eligible for orphan-drug

designation at the time of submission of the request therefor" (21 CFR § 316.29(a)).

FDA responded to Sidelines's argument that 17P's orphan drug designation should be revoked because its sponsor relied on government-funded research by explaining that "new research on its own is not what the [Orphan Drug Act] seeks to achieve" (Kux 2011). Relying on government-funded research is consistent with the Act's aim of encouraging commercialization of orphan drugs. To Sidelines's argument that a grant of market exclusivity to 17P would result in a period of unjustified cost increase, FDA responded that this too comported with the intent of Congress (ibid.).

Its professed lack of discretion notwithstanding, FDA found a way to take action. On March 30, 2011, the agency issued a press release in which it explained in the first paragraph that "KV Pharmaceuticals, the drug's owner, received considerable assistance from the federal government in connection with the development of Makena by relying on research funded by the National Institutes of Health to demonstrate the drug's effectiveness" (FDA 2011). The agency went on to announce that it would not enforce K-V's statutory right to seven years of marketing exclusivity. The Centers for Medicare & Medicaid Services (CMS) issued a statement the same day, announcing that compounded 17P could be reimbursed by Medicaid (CMS 2011).

On April 1, 2011, K-V issued a press release of its own, announcing that it had decided to, among other things, reduce the list price of Makena from $1,440 to $690 and expand the company's patient assistance program (K-V Pharmaceutical 2011). K-V noted that "85 percent of patients will pay $20 or less per injection for FDA-approved Makena, and patients whose financial need is greatest would receive FDA-approved Makena at no out-of-pocket cost" (ibid.). It was widely viewed as too little too late. On August 4, 2012, the manufacturer declared bankruptcy, blaming in its press release "a lack of enforcement of the orphan drug exclusivity granted" to Makena[1] (K-V Pharmaceutical 2012). On July 5, 2012, K-V sued FDA, challenging the agency's decision to decline to take enforcement action against pharmacies that compound 17P (Karst 2014). Two years later, in July 2014, K-V agreed to dismiss the case, without making public what, if anything, FDA promised in return (ibid.).

V. ADJUSTING THE ORPHAN DRUG ACT'S BALANCE IN FAVOR OF ACCESS

A. Shortening the Exclusivity Period

One way that Congress could adjust the Orphan Drug Act's balance between encouraging innovation, on the one hand, and ensuring access, on the other, would be to shorten the exclusivity period, whether across the board or on the basis of predetermined criteria. A reduction in the exclusivity period could be paired with an alternative incentive that does not affect access, such as the priority review vouchers that are already available for rare pediatric diseases and for certain tropical diseases (Mueller-Langer 2013:192–93).

An across-the-board reduction in the exclusivity period would have the advantage of ease of administration for the government and predictability for industry. There is the possibility, though, that manufacturers faced with a shorter amount of time in which to recoup their investments and earn profits would set prices proportionately higher. An across-the-board reduction would also fail to account for factors such as whether the drug was already available in compounded or generic form.

In 1992, Congress considered an amendment to the Orphan Drug Act that would have allowed for two years of guaranteed exclusivity, after which competing drugs could be approved if, at any point in the next seven years, sales of the originator drug topped $200 million (Pulsinelli 1999:332). The European Union has adopted an approach akin to this. There, the orphan-drug exclusivity period can be shortened from ten years to six if the orphan-drug designation criteria are no longer met (Michaux 2010:661). A regime in which Congress, or FDA with Congress's authorization and guidance, provided for a shortened exclusivity period when a drug reached a predetermined level of sales, profit, or return on investment, or met other criteria, would be more calibrated than an across-the-board reduction, but it could be difficult to administer and would have the downside of undermining predictability. Perhaps a more fundamental concern is that, after Makena, payers may balk at any period of monopoly pricing for drugs that are already available to patients in compounded or generic form.

B. Allowing for Limited Competition During the Exclusivity Period

Over the years, a number of amendments to the Orphan Drug Act have been proposed that would authorize two or more companies to sell an orphan drug during the seven-year exclusivity period (Pulsinelli 1999:324). Instead of a monopoly, the market would take the form of an oligopoly. Prices would still be supracompetitive during the exclusivity period, but they would not be as high as they are under the current system. In 1990, Congress passed a set of amendments that, among other things, would have allowed companies that simultaneously developed the same orphan drug to share exclusivity (ibid., 325). The amendments were vetoed by then-President George H. W. Bush, who was concerned about their potential to undermine the act's incentive structure (ibid., 337).

Gary Pulsinelli has raised the possibility that, to a manufacturer, shared exclusivity might be "practically indistinguishable from straight competition," which could in turn "lead to investment at less than the optimal level" (ibid., 328). On the other hand, there is the possibility that, to consumers, shared exclusivity might look a lot like exclusivity. Pulsinelli gives the example of human growth hormone, which at one time was manufactured by two different companies that "essentially" shared exclusivity (ibid., 326). Human growth hormone was nonetheless "one of the highest priced and most profitable orphans, for both companies" (ibid.).

One way to address concerns that the incentive for sponsors to engage in orphan drug research and development be preserved would be to lengthen the exclusivity period in those cases in which there is limited competition. Another variant would be to allow for limited competition postapproval but only after a drug reached a certain predetermined level of sales, profit, or return on investment. Both of these variations would have a cost in terms of access, though.

C. Implementing a Cap on Drug Prices

A cap on the price that an orphan drug's manufacturer can charge during the period of exclusivity is the most straightforward approach to adjusting the balance between innovation and access. Price caps would

also have the advantage of moderating prices from day one. Setting, applying, and enforcing them could pose political and practical difficulties for Congress and FDA, however. Before 1995, the NIH included a term in the contracts it entered into with partners in the life-sciences industry that required that there be "a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public" ("PHS/NIH Abandons . . ." 1995). The term was widely believed to be a deal breaker, preventing public–private partnerships from forming at all (ibid.).

In an article in *Health Affairs*, Ana Valverde (2012:2530) and colleagues proposed what they called the "grant-and-access pathway," under which grants would be available to support early phase orphan-drug development. Companies that opted in to this pathway and were awarded grants would not be able to claim the Orphan Drug Act's tax credits (ibid.). Of more significance, they would have to agree to price caps, which would be set "based on how long drug development took and how much it cost, expected market size, and the target internal rate of return" (ibid.). The authors' analysis revealed that "[i]n the absence of a robust grant program, the ultra-orphan drug developer in our example would need to increase drug prices to $329,000 per patient for an annual course of treatment to yield a 20 percent rate of return" (ibid., 2531). By contrast, under the grant-and-access pathway, 75 percent of the development costs, estimated at $4.5 million in their model, would be covered. This would mean that the ultra-orphan drug developer would yield a 20 percent return on its investment at "a treatment price of $84,750 per patient—roughly one-fourth of the cost estimated under the current pathway" (ibid., 2531–32). Because the grant-and-access pathway proposed by Valverde and colleagues is optional, it might not pose some of the political difficulties price caps usually present. Another advantage of the grant-and-access pathway is that it would leave undiluted the incentive provided by the Orphan Drug Act's grant of seven years of market exclusivity. A significant downside of the pathway is that it would only increase access in those cases in which orphan drug developers agreed to its terms.

D. Authorizing FDA to Address Access Concerns on a Case-by-Case Basis

A fourth possibility would be to preserve as the default the Orphan Drug Act's current balance between incentivizing innovation and

ensuring access, while permitting FDA to make adjustments on a case-by-case basis. FDA could be given the authority to decide in each case whether and for how long to award market exclusivity, taking into account factors such as the need to provide a reasonable reward for a company's investment, the degree to which the application for marketing approval relies on government research, the public health benefits of the drug at issue, and whether the drug is already available in compounded or generic form. Alternatively, or in addition, FDA could be given the authority to decide in each case whether an orphan drug, given its price, reimbursement profile, and other factors, is sufficiently accessible to patients.

Currently, FDA does not consider the questions of price and access that the Makena case posed, not typically at least, or through a mechanism other than the exercise of its enforcement discretion. The agency does administer the statutory exclusivity period that gives orphan drug developers monopoly-pricing power, but the statute affords it little discretion. As noted earlier, the regulations implementing the Orphan Drug Act provide that "a sponsor of a drug that is otherwise the same drug as an already approved orphan drug may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug" (21 CFR § 316.20(a)). When the regulations were adopted, several commenters "argued that FDA must recognize the effect of price on access to patient care and urged that cost considerations must be used in determining whether a subsequent drug makes a major contribution to patient care" (Orphan Drug Regulations, 57 Fed. Reg. 62076, 62078 (Dec. 29, 1992)). FDA declined to so hold, explaining that "[a]lthough FDA understands that costs can indeed have a major impact on access to a drug, FDA has no authority over drug pricing or any authority to consider it in drug approval" (ibid., 62079).

FDA was also asked to factor in cost when determining whether "sufficient quantities" of the drug are not available "to meet the needs of persons with the disease or condition for which the drug was designated" (21 USC § 360cc(b)(1)). The agency responded that it "does not have the authority under existing law to equate high cost with lack of sufficient quantities, even though cost may affect access to a drug" (Orphan Drug Regulations, 57 Fed. Reg. 62076, 62084 (Dec. 29, 1992)).

A case-by-case approach to awards of exclusivity would allow for calibration, but it would come at a cost to the predictability of the regulatory process. This could in turn reduce the level of investment in orphan drug research and development. A formal mechanism for challenging the high price of orphan drugs would have the advantage of preserving the basic structure of the current system, but it, too, could reduce companies' incentive to bring orphan drugs to market. It also seems highly unlikely to attract political support. If patients and providers were limited to challenging the adequacy of companies' patient assistance programs, the effect on incentives would be minimized. Allowing for such challenges could be particularly valuable in cases in which the nature of the drug or the patient population were such that it would be difficult to mount an advocacy campaign of the sort that was successful in the Makena case.

If the Orphan Drug Act is amended to allow access-based challenges, an agency or entity other than FDA, with its historic focus on safety and efficacy, should be charged with adjudicating the claims. In the European Union, the decision to grant market authorization is made by one agency and the decision to grant reimbursement is made by another. Eline Picavet and colleagues (2012) note that "[m]arket authorization does not automatically mean central funding of, and access to, an orphan drug."

VI. CONCLUSION

The Makena case drew attention to the high price that patients, providers, the government, and other payers pay for the relatively small gains that accrue when a recycled molecule becomes an FDA-approved orphan drug. Eliminating or shortening the period of exclusivity would result in orphan drugs that might otherwise have been adopted by a private-sector sponsor going unstudied or remaining unapproved by FDA. Adjusting the period for some but not all drugs leads to the difficult question of where to draw the line and would undermine predictability, which is key to encouraging investment. A formal mechanism to challenge the adequacy of a company's patient assistance program is potentially a more promising reform.

There can be gains to public health associated with FDA approval even of "recycled molecules" like Makena that were previously

available to patients in compounded form. For one, FDA-approved drugs are available through standard commercial channels, which eases access. In addition, drugs manufactured according to good manufacturing practices are more likely to be pure and to have the desired potency than drugs that are compounded (Patel and Rumore 2012:410). The risk of contamination is higher for sterile injectables like Makena than it is for other drug forms. While these are real benefits, they are not invaluable. Even if the status quo is maintained, going forward companies will surely keep the Makena case in mind when pricing recycled molecules.

NOTE

1. In May 2013, the *Wall Street Journal* reported that sales of Makena were surging (Gleason 2013). In September 2013, the *St. Louis Post-Dispatch* reported that K-V Pharmaceutical had emerged from bankruptcy (Brown 2013).

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