

2013

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### Recommended Citation

Sumin Kim, *The Orphan Drug Act: How the FDA Unlawfully Usurped Market Exclusivity*, 11 NW. J. TECH. & INTELL. PROP. 541 (2013).  
<http://scholarlycommons.law.northwestern.edu/njtip/vol11/iss6/3>

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**The Orphan Drug Act:  
How the FDA Unlawfully Usurped Market Exclusivity**

*Sumin Kim*



# The Orphan Drug Act: How the FDA Unlawfully Usurped Market Exclusivity

By Sumin Kim\*

*The Board of KV Pharmaceutical bet the company on the success of Makena®, a pre-term birth drug. However, in the midst of a public outcry over the excessive pricing of Makena®, the FDA declared that it would not honor the market exclusivity that KV Pharmaceutical had obtained for Makena® under the Orphan Drug Act. As a result, KV Pharmaceutical filed for Chapter 11 bankruptcy. This Note analyzes the situation under the lens of the Takings Clause of the Fifth Amendment. Specifically, I argue that market exclusivity for Makena® was private property and thus, the FDA unlawfully usurped KV Pharmaceutical's private property without just compensation.*

## I. INTRODUCTION

¶1 In 2011, KV Pharmaceutical (“KV”) drew the public ire for pricing Makena®, a preterm birth drug, at roughly seventy-five times the price of the generic, shortly after receiving seven years of market exclusivity under the Orphan Drug Act.<sup>1</sup> In addition to the excessive price hike, which put the drug out of reach for many qualified patients, people were enraged that KV had the gall to use a taxpayer-funded study to prove the safety and effectiveness of Makena®, only to turn around and try to reap monopoly rents from taxpayers.<sup>2</sup> The Food and Drug Administration (the “FDA”) subsequently announced that it would not regulate pharmacies that compounded the generic version of Makena®, and it supported its stance by pointing out that KV relied on research funded by the National Institutes of Health.<sup>3</sup>

¶2 At first glance, the situation seems like another iteration of a greedy drug company trying to make windfall profits. Although KV did not act illegally, there is a gut sense that its actions were wrong. Hence, it is very easy to agree with the FDA’s decision to exercise enforcement discretion concerning Makena®. However, this Note takes the opposite stance in arguing that the FDA was wrong to exercise its enforcement discretion. The basis for the argument lies in the Takings Clause of the Fifth Amendment. By refusing to enforce market exclusivity, the FDA effectively usurped property from KV without just compensation. In support of the argument, this Note looks to the legislative, executive, and judicial intent behind the Orphan Drug Act.

¶3 Section II describes the impetus behind the Orphan Drug Act and analyzes how Congress has amended and the FDA has implemented the Act. The analysis in Section II

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<sup>1</sup> Andrew Zajac, *Drug Maker Lowers Price of Makena Pregnancy Drug to \$690 per Dose*, L.A. TIMES, Apr. 1, 2011, <http://articles.latimes.com/2011/apr/01/news/la-pn-makena-price-cut-fda-20110401>.

<sup>2</sup> *Id.*

<sup>3</sup> *FDA Statement on Makena*, U.S. FOOD & DRUG ADMIN. (Nov. 8, 2011), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm279098.htm>.

reveals that the legislative and executive branches of government have been very consistent in upholding and promoting the financial incentives, and particularly the market exclusivity provision, of the Orphan Drug Act. Section III provides the tumultuous history of Makena®, and in the process, shows that contrary to the public discourse, Makena® is not fully accepted by the medical community as a safe and effective drug for preterm birth. Since the FDA's *modus operandi* is to protect the public, this finding suggests that Makena® is exactly the type of drug that needs FDA approval and oversight. Sections IV and V delve into the debate behind the FDA's decision to approve Makena®, and in doing so, further reveal the uncertainty surrounding the drug's safety. Like Section III, this uncertainty surrounding Makena® suggests that it is exactly the type of drug that needs FDA oversight. Finally, Section VI advances the Fifth Amendment Takings Clause argument to reach the conclusion that the FDA was wrong to exercise its enforcement discretion.

## II. THE ORPHAN DRUG ACT

¶4 Today, an estimated ten to twenty million people in the United States suffer from some type of a rare disease,<sup>4</sup> which Congress has defined as a disease affecting 200,000 people or less.<sup>5</sup> For pharmaceutical companies, the limited population size serves as a financial disincentive for the development of drugs for rare diseases. This disincentive is entirely understandable, since on average, it is estimated to cost more than \$300 million and ten years to bring a drug to market.<sup>6</sup> With only 200,000 potential customers, a drug company would have a difficult time simply recouping the cost of development.

¶5 The financial disincentives of developing drugs for rare diseases are so compelling that even when a compound is already identified as a possible treatment, pharmaceutical companies will not pursue it.<sup>7</sup> To make matters worse, many potential treatments are not patentable because the compounds are often discovered during the course of research on different drugs, and their potential use in the treatment of rare diseases is discussed in printed publications.<sup>8</sup> When patent protection is unavailable, firms are even less willing to invest in the development of a drug, because a copycat firm could then free-ride off the investment and underprice the first firm.<sup>9</sup> Consequently, many therapeutic compounds are left without a sponsor to conduct the clinical trials necessary for FDA approval. In the medical community, these drugs without sponsors have become known as "orphans."<sup>10</sup>

¶6 In the early 1980s, Congress began to take an interest in orphan drugs. In the aggregate, rare diseases were affecting between ten and twenty million people in the

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<sup>4</sup> Gary A. Pulsinelli, *The Orphan Drug Act: What's Right With It?*, 15 SANTA CLARA COMPUTER & HIGH TECH. L.J. 299, 305 (1999).

<sup>5</sup> David D. Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L.J. 125, 125 (2000).

<sup>6</sup> Pulsinelli, *supra* note 4, at 304.

<sup>7</sup> Rohde, *supra* note 5, at 126.

<sup>8</sup> *Id.* at 127 (saying, in fn. 12, that printed publications are considered prior art and would preclude an idea from being patented).

<sup>9</sup> Pulsinelli, *supra* note 4, at 304.

<sup>10</sup> Rohde, *supra* note 5, at 125.

United States.<sup>11</sup> As a result, by 1983 Congress passed and implemented the Orphan Drug Act<sup>12</sup> (the “Act”) in order to incentivize the development of drugs for rare diseases.

### A. *Legislative Intent*

¶7 An analysis of the proposed and accepted amendments to the Act reveals that Congress has, except on one occasion, advocated the use of financial incentives, especially market exclusivity, to promote the development of orphan drugs. This advocating of financial incentives has come even with the recognition that drug companies could take advantage of the Act for excessive profits. Such an end is not within the spirit of the Act, but is nevertheless legal. The analysis first focuses on market exclusivity and then looks to other provisions of the Act in general.

#### 1. Market Exclusivity

¶8 The cornerstone of the Act is the seven years of market exclusivity that an orphan drug sponsor receives upon FDA approval for its drug.<sup>13</sup> Market exclusivity can be achieved because the FDA must approve all drugs that are marketed in the United States.<sup>14</sup> Thus, by refusing to approve a similar drug for seven years, the FDA can effectively create a monopoly for an orphan drug.<sup>15</sup>

¶9 However, there are two exceptions to market exclusivity. The first is when a sponsor cannot “assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease.”<sup>16</sup> The second is when a sponsor agrees to share the market with another firm.<sup>17</sup> It seems significant that Congress specified only two exceptions to market exclusivity, especially since Congress did not create any limitations on the pricing of orphan drugs. A law that goes beyond patent protection and guarantees a monopoly market is clearly a potential target for abuse. Yet, Congress did not include any safety valves that would allow the FDA to limit market exclusivity in case a sponsor was able to excessively profit off an orphan drug.<sup>18</sup> To the contrary, numerous amendments were proposed that aimed to limit the ability of drug companies to make excessive profits. Yet, none of those amendments to market exclusivity were ever passed.<sup>19</sup>

¶10 In 1990, Congress came very close to limiting market exclusivity,<sup>20</sup> but President Bush pocket-vetoed the amendments. The President stated that he did not want to

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<sup>11</sup> Pulsinelli, *supra* note 4, at 305.

<sup>12</sup> 21 U.S.C. § 301 (2006).

<sup>13</sup> *Id.* § 360cc.

<sup>14</sup> See Jesse M. Boodoo, *Compounding Problems and Compounding Confusion*, 36 AM. J.L. & MED. 220, 231 (2010) (noting that all drugs are regulated under the Federal Food, Drug, and Cosmetic Act).

<sup>15</sup> The FDA could still approve the exact same drug for another indication. However, the monopoly would be effective at least with regard to the application of the drug to the specific disease.

<sup>16</sup> 21 U.S.C. § 360cc(b)(1) (2006).

<sup>17</sup> *Id.* § 360cc(b)(2).

<sup>18</sup> The Act was not envisioned as a way for drug companies to make a lot of profit.

<sup>19</sup> Pulsinelli, *supra* note 4, at 324-36.

<sup>20</sup> See 136 CONG. REC. H5799 (daily ed. July 30, 1990). The amendment would have permitted simultaneous licensing of the same orphan product for the same indication if (i) the second company requests orphan designation within six months of publication by the FDA of its action to designate the drug for the first company; (ii) the second company initiates human clinical trials not more than twelve months

endanger the Act's success, which he believed was driven primarily by the incentive of market exclusivity.<sup>21</sup> Representative Henry A. Waxman, who was responsible for drafting the 1990 Amendments, tried again in 1994 to place limits on market exclusivity.<sup>22</sup> However, this time, Congress failed to act upon the proposed amendments, reflecting a shift back towards favoring unfettered market exclusivity for orphan drugs.<sup>23</sup>

## 2. Amendments

¶11 In the first version of the Act, Congress included two provisions that reflected a desire to promote orphan drugs, but which were unsuccessful in doing so.<sup>24</sup> First, Congress gave the FDA the discretion to determine whether a disease was rare, or in other words, to decide whether there was any reasonable expectation of recovering the cost of development.<sup>25</sup> Second, in order to qualify as an orphan drug, the drug had to be unpatentable and unpatented.<sup>26</sup> These two provisions were subsequently amended to more effectively promote development of orphan drugs.

¶12 In 1984, Congress eliminated the “reasonable cost of development” provision and redefined “orphan” to mean any drug that had a target population of 200,000 persons or less.<sup>27</sup> The amendment was in response to drug companies’ reluctance to sink money into estimating cost, only to be rejected and have information about their operations revealed.<sup>28</sup> In 1985, Congress further reduced the requirements for obtaining orphan drug status by eliminating the patent provisions.<sup>29</sup> Again, the amendment was in response to the lack of firm activity regarding orphan drugs.<sup>30</sup> When the Act was first passed, Congress believed that patent law would be sufficient to incentivize the development of patentable and patented orphan drugs.<sup>31</sup> While in reality, many potential orphan drugs were under patents that either had expired or had very little patent time left, meaning firms did not want to invest in the development of these drugs because they would have no guarantee of recouping their investment.<sup>32</sup> Furthermore, it was difficult to determine

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after the first company initiated clinical trials; and (iii) the second company submits an approvable new drug application to the FDA no more than one year after the first company submits its new drug application.

<sup>21</sup> Gerald Mossinghoff, President of the Pharmaceutical Manufacturers Association, stated that “by far the most important incentive offered by the Orphan Drug Act” is market exclusivity. *Waxman Bill Limits Seven-Year Exclusivity Granted Orphan Drugs*, BIOTECH. NEWSWATCH, May 7, 1990, at 4.

<sup>22</sup> See H.R. 4865, 103d Cong. (1994), available at <http://www.gpo.gov/fdsys/pkg/BILLS-103hr4865rh/pdf/BILLS-103hr4865rh.pdf>. See also *Orphan Drugs*, WAXMAN.HOUSE.GOV, <http://waxman.house.gov/orphan-drugs> (last visited Nov. 4, 2011).

<sup>23</sup> *Id.*

<sup>24</sup> See Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1982) (codified as amended at 21 U.S.C. §§ 360aa–360ee (1994)).

<sup>25</sup> Pulsinelli, *supra* note 4, at 306.

<sup>26</sup> *Id.* The FDA interpreted the patent requirements to mean that an orphan drug can receive approval when (1) no use or product patent has been issued or (2) no use patent has been issued and the product patent has expired. H.R. REP. NO. 99-153, at 3-4 (1985).

<sup>27</sup> Health Promotion and Disease Prevention Amendments of 1984, Pub. L. No. 98-551, 98 Stat. 2815 (1984).

<sup>28</sup> See Pulsinelli, *supra* note 4, at 307.

<sup>29</sup> See Orphan Drug Amendments of 1985, Pub. L. No. 99-91, 99 Stat. 387 (1985).

<sup>30</sup> Pulsinelli, *supra* note 4, at 308.

<sup>31</sup> H.R. REP. NO. 99-153, at 3 (1985).

<sup>32</sup> *Id.* at 4. As discussed *supra* note 26, the FDA was willing to approve an orphan drug that had an

whether a drug was patentable, making it time-consuming for an orphan drug to go through the approval process.<sup>33</sup> In 1988, Congress again amended the Act to require firms to notify the FDA one year in advance of discontinuing the production of an orphan drug, so that the FDA would have enough time to find another manufacturer.<sup>34</sup>

¶13 Two themes become apparent from the amendments to the Act. First, Congress understood the need to provide certainty in the approval process for orphan drugs. Naturally, if the FDA had sole discretion in determining the legitimacy of a forecasted market for an orphan drug, potential sponsors would be deterred from sinking an investment into pursuing that drug because of uncertainty. This deterrence especially holds true for orphan drugs because they do not have high profitability potential to begin with. Thus, by creating a bright line rule of 200,000 persons or less in order to qualify as an orphan, and thereby creating an environment of regulatory certainty, Congress was attempting to reduce the barriers to orphan drug development. The same initiative was seen in the amendments to the patent provisions in 1985. By removing the patentability requirement, Congress was creating a more predictable process for potential orphan drug sponsors.

¶14 The second theme to emerge, and one that served as the impetus for the first, is that Congress was determined to bring orphan drugs to market. Prior to the 1985 Amendments, the Committee on Energy and Commerce (the “Committee”), overseeing the proposed amendments, was well aware that firms could profitably abuse the Act by taking advantage of the seven years of market exclusivity.<sup>35</sup> Thus, the Committee fully understood that removing the patent provisions would only increase the potential for abuse, since it would be easier to obtain orphan drug status. Despite this problem, the Committee “decided that it would still recommend the amendment because it was viewed as an important incentive for the development of orphan drugs.”<sup>36</sup> Congress agreed and the amendments were soon adopted. Over the next two years, the Committee monitored the orphan drug situation and in December of 1987, recommended that amendments be made to limit the market exclusivity provision of the Act.<sup>37</sup> However this time, Congress did not agree. Instead, Congress reemphasized its resolve in bringing orphan drugs to market when it passed the notification requirement. Effectively, Congress was signaling to the drug industry that it wanted the public to have stable and continuous access to orphan drugs, even at the risk of potential abuse.

¶15 In conclusion, it seems pretty clear that Congress was determined to bring orphan drugs to market by providing certainty in the approval process. Moreover, the fact that Congress was willing to create a bright line rule, even if the rule was overly inclusive (of potentially profitable orphan drugs, i.e. drugs that do not need financial incentives), suggests that Congress was willing to risk a few years of overpriced drugs in order to save lives.<sup>38</sup>

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expired *product* patent. This gave firms an incentive to wait until the patent expired, which further prolonged the development of orphan drugs.

<sup>33</sup> Pulsinelli, *supra* note 4, at 308.

<sup>34</sup> *Id.* at 309; 21 C.F.R. § 316.23 (1999).

<sup>35</sup> See H.R. REP. NO. 100-473, at 6 (1987).

<sup>36</sup> *Id.*

<sup>37</sup> *Id.* at 6–7.

<sup>38</sup> See Pulsinelli, *supra* note 4, at 318 (“[T]he real tradeoff . . . is between having expensive drugs and having no drugs for these diseases.”).

### 3. Other Provisions

¶16 In addition to market exclusivity, the Act provides many other financial incentives as well. First, orphan drug sponsors can request FDA assistance in navigating the complex and costly approval process.<sup>39</sup> Second, orphan drug sponsors can manufacture their drug prior to receiving full FDA approval.<sup>40</sup> Third, orphan drug sponsors receive a tax credit for fifty percent of the amounts spent on clinical trials.<sup>41</sup> And finally, sponsors are eligible for federal grants to help defray the costs of clinical testing.<sup>42</sup> All of these financial incentives clearly indicate that Congress has been determined to promote the development of orphan drugs.

¶17 Along those same lines, Congress has also indicated its desire to promote orphan drugs by the amendments that it did *not* pass. For example, an amendment was proposed in 1990 that would tax any revenue from orphan drugs once a firm was able to recapture twice the drug's development costs plus twenty-five percent of annual profit.<sup>43</sup> The legislation was an attempt to curb the profit making potential of orphan drugs. In 1991, the 1990 Amendment was modified and re-proposed, calling for a seventy-five percent tax on all profits once development costs had been recovered.<sup>44</sup> Again the proposal did not find support within Congress. In 1993, the amendment was again modified and rejected, this time calling for a seventy-five percent tax on all profits in excess of 125 percent of production costs, but only after all development costs had been recovered.<sup>45</sup> The failure of these proposals to make their way into legislation indicates that Congress has not been afraid to use financial incentives to promote the development of orphan drugs.

#### B. FDA Intent

¶18 In January 1993, almost ten years after the Act was implemented, the FDA finally passed regulations for administering the Act.<sup>46</sup> In the Orphan Drug Regulations (the "Regulations"), the FDA formally laid out the rules by which it was administering the Act and also addressed various concerns that came from both the drug industry and associations representing patients with rare diseases.<sup>47</sup> The FDA's responses to those concerns revealed that it was fully aligned with Congress's preference for financial incentives. Moreover, a careful look at the Regulations confirmed likewise.

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<sup>39</sup> See 21 U.S.C. § 360aa (1994) (the FDA will advise on what tests and experiments are required and how to effectively design clinical trials).

<sup>40</sup> See *id.* § 360dd.

<sup>41</sup> See 26 U.S.C. § 45C (Supp. II 1994).

<sup>42</sup> See 21 U.S.C. § 360ee. See also Pulsinelli, *supra* note 4, at 313 (indicating the costs were originally limited to human testing, but later expanded in the 1988 Amendments to include all testing).

<sup>43</sup> See 136 CONG. REC. H6194 (daily ed. Apr. 10, 1990) (statement of Rep. Stark). See also Rohde, *supra* note 5, at 137.

<sup>44</sup> See 137 CONG. REC. E1171 (daily ed. Apr. 10, 1991) (remarks of Rep. Stark reintroducing the Orphan Drug Windfall Profits Tax Act of 1991). See also Pulsinelli, *supra* note 4, at 336.

<sup>45</sup> See 139 CONG. REC. H1851 (daily ed. Apr. 1, 1993) (remarks of Rep. Stark regarding amendments to the Orphan Drug Windfall Profits Tax Act). See also Pulsinelli, *supra* note 4, at 336.

<sup>46</sup> See Orphan Drug Regulations, 57 Fed. Reg. 62076 (Dec. 29, 1992) (to be codified at 21 C.F.R. pt. 316).

<sup>47</sup> *Id.*



¶19 One concern was that improvements in diagnostics and screening technologies would result in patient populations much greater than that initially anticipated for orphan drugs.<sup>48</sup> In other words, an orphan drug could potentially serve a patient population greater than 200,000 people and become very profitable, but remain an orphan because there was no way to revoke orphan status. However, the FDA said that it had no way of determining the likely treatment population and thus, kept the bright line rule of 200,000 people as determined by current diagnostic methods.<sup>49</sup>

¶20 A similar concern suggested that market exclusivity be withdrawn if an orphan drug later proved to have commercial potential or exceeded the 200,000-patient threshold.<sup>50</sup> But in response, the FDA deferred to President Bush's pocket-veto in 1990 that otherwise would have authorized the FDA to revoke an approval for such reasons.<sup>51</sup> The FDA's response to both this concern and the one above was codified in 21 C.F.R. § 316.29, which lists the conditions under which the FDA can revoke an orphan drug designation. The three conditions are: (1) if the request for designation contained an untrue statement of material fact, (2) if the request omitted material information, or (3) if the drug in fact had not been eligible for orphan drug status at the time of submission of the request.<sup>52</sup> Prominently missing from this list is any condition regarding patient population or profitability, reflecting a strong preference for incentives. Furthermore, 21 C.F.R. § 316.29(c) explicitly states that an orphan drug designation cannot be revoked for reasons concerning post-approval patient population. Clearly, the FDA wanted to stay away from restricting market exclusivity.

¶21 The concerns about orphan drug profitability have been driven mainly by five drugs: zidovudine (treatment for HIV), pentamidine isethionate (treatment for pneumonia associated with AIDS), human growth hormone (treatment for improper growth in children lacking the hGH enzyme), erythropoietin (treatment for anemia associated with end-stage renal disease), and Ceredase® (treatment for Gaucher's disease).<sup>53</sup> All of these drugs were wildly profitable, yet the FDA did not fail to enforce market exclusivity for these drugs, perhaps recognizing the fact that having a drug is better than having no drug at all.<sup>54</sup> Drug companies, like all private companies, are in the business of generating profits. Since orphan drugs typically do not yield large returns on investment, they have a hard time attracting the eyes of potential sponsors. If the FDA made it a common practice to limit the profitability of orphan drugs, the financial incentives built into the Act would be undercut. Orphan drugs would be even more unattractive to potential sponsors looking for the next big revenue generator.

¶22 Moreover, since 1983 the Act has "successfully enabled the development and marketing of more than 400 drugs and biologic products for rare diseases,"<sup>55</sup> which means that the five blockbuster drugs mentioned above represent less than two percent of

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<sup>48</sup> *Id.* at 62081.

<sup>49</sup> *Id.*

<sup>50</sup> *Id.* at 62802

<sup>51</sup> *Id.* A drug can be orphaned if it (1) has a patient population less than 200,000 or (2) has no commercial potential even though its patient population is greater than 200,000.

<sup>52</sup> 21 C.F.R. § 316.29 (2011).

<sup>53</sup> See Pulsinelli, *supra* note 4, at 316–17.

<sup>54</sup> See *id.* at 318.

<sup>55</sup> *Developing Products for Rare Diseases & Conditions*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/forindustry/developingproductsforrare diseasesconditions/default.htm>.

all orphan drugs. In the words of the FDA, it tried “as much as possible [in implementing the Regulations] to protect the incentives of the Orphan Drug Act without allowing their abuse.”<sup>56</sup>

¶23 In conclusion, although the Act was not created to be a vehicle for drug companies to generate windfall profits, the FDA has recognized the importance of financial incentives and thus, has not tried to undercut the Act, despite the fact that the Act’s market exclusivity provision is ripe for abuse. Rather, the FDA enacted the Regulations with a conscious effort towards giving the financial incentives of the Act their full effect (only protecting against false information).

### III. HISTORY OF MAKENA®

¶24 “Makena is a prescription hormone medicine (progesterin) used to lower the risk of preterm birth in women who are pregnant with one baby and who have delivered another baby too early (preterm) in the past.”<sup>57</sup> Chemically, the active ingredient in Makena® is 17 alpha-hydroxyprogesterone caproate (“17P”).<sup>58</sup>

¶25 The FDA first approved the drug 17P in 1956, under the name Delalutin®.<sup>59</sup> The approval was based on a finding of safety, but not effectiveness.<sup>60</sup> In 1971, the indications for Delalutin® were reviewed for efficacy, in accordance with the new Drug Efficacy Study Implementation program.<sup>61</sup> In its review, the FDA stated that 17P was “probably” effective for habitual and threatened abortion.<sup>62</sup> However, in 1973, the FDA reversed its prior conclusion that 17P was an effective treatment for habitual and threatened abortion.<sup>63</sup> In addition, the FDA gave notice that a new study had found a possible correlation between the use of prenatal hormonal treatment and congenital heart defects in offspring.<sup>64</sup> As a result, all pregnancy-related indications were removed from the labeling for Delalutin®.<sup>65</sup>

¶26 In 1977, the FDA went one step further and required all progestational drug products (except for use in contraceptives) to be labeled with a contraindication for pregnancy.<sup>66</sup> The FDA’s decision was based on several reports indicating that the use of sex hormones, including 17P, during early pregnancy could cause serious damage to offspring.<sup>67</sup> But in 1999, the FDA revoked its contraindication requirement for

<sup>56</sup> Orphan Drug Regulations, 57 Fed. Reg. at 62077.

<sup>57</sup> *What is Makena?*, MAKENA, <http://www.makena.com/pages/dtc/already-pregnant/what-is-makena.aspx> (last visited Apr. 7, 2013).

<sup>58</sup> Makena® used to be called Delalutin®. *See also 17 alpha-hydroxyprogesterone caproate*, OBFOCUS, <http://www.obfocus.com/reference/Formulary/Drugs%20in%20Pregnancy/17OHPC.htm> (last updated Oct. 18, 2007).

<sup>59</sup> *17-Hydroxyprogesterone*, WIKIPEDIA, [http://en.wikipedia.org/wiki/17-Hydroxyprogesterone#cite\\_note-14](http://en.wikipedia.org/wiki/17-Hydroxyprogesterone#cite_note-14) (last modified Feb. 27, 2013).

<sup>60</sup> Determination That Delalutin Was Not Withdrawn from Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. 36419 (F.D.A. June 25, 2010) (indicating the original labeling states that Delalutin “appears to be useful” for the listed indications).

<sup>61</sup> *Id.* at 36420.

<sup>62</sup> *Id.*

<sup>63</sup> *Id.*

<sup>64</sup> *Id.*

<sup>65</sup> *Id.*

<sup>66</sup> *Id.*

<sup>67</sup> *Id.*

progestational drug products, claiming that such labeling was not warranted based on a review of the data.<sup>68</sup> Less than one month later, Bristol-Myers Squibb requested a withdrawal of its New Drug Application (NDA) for Delalutin®, claiming that the drug had not been marketed for several years.<sup>69</sup> On September 13, 2000, the FDA officially withdrew its approval for Delalutin®.<sup>70</sup>

¶27 Although 17P lost FDA approval for use in pregnancy, a study conducted in 2003 by the National Institute of Child Health and Human Development (NICHD) found that contrary to prior studies, 17P was effective in treating preterm births, with no significant difference in the occurrence of genital malformations in children who had been exposed to 17P as compared to children who had been exposed to a placebo.<sup>71</sup> Based on this new study, 17P for use in pregnancy made a comeback (though illegally since FDA approval had been withdrawn), with compounding pharmacies providing generic versions of 17P at \$10 to \$20 per dose.<sup>72</sup> Since a woman was expected to take a weekly injection for about twenty weeks, the total price of 17P was about \$400.

¶28 Perhaps recognizing the re-emerging market for 17P in treating preterm birth, CUSTOpharm, Inc. requested that the FDA determine whether approval for Delalutin® was withdrawn for reasons of safety or effectiveness.<sup>73</sup> If approval had been withdrawn for either of these reasons, then according to 21 C.F.R. § 314.161,<sup>74</sup> 17P would not be available for an Abbreviated New Drug Application (ANDA).<sup>75</sup> Subsequently, the FDA decided that Delalutin® had not been removed for safety and effectiveness reasons and thus, would remain on the list of previously approved drugs and be available for an ANDA.<sup>76</sup>

¶29 However, Adeza Biomedical Corporation was the eventual company to file an ANDA (under the drug name Gestiva™) for 17P with the FDA.<sup>77</sup> Recognizing the gravity of the estimated \$18 billion in costs associated with preterm births in 2003, the FDA granted Priority Review to Adeza's application. The agency set a goal to complete its review or otherwise respond to the application by October 20, 2006.<sup>78</sup> On August 29,

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<sup>68</sup> *Id.*

<sup>69</sup> *Id.*

<sup>70</sup> *Id.*

<sup>71</sup> Women who received 17P treatment had a preterm birth rate of 36.3% versus 54.9% in women who received a placebo. *17 alpha-hydroxyprogesterone caproate*, *supra* note 58.

<sup>72</sup> Daniel J. DeNoon, *FDA: Pharmacies Can Still Make Preterm Birth Drug*, WEBMD (Mar. 30, 2011), <http://www.webmd.com/baby/news/20110330/fda-generic-makena-ok>.

<sup>73</sup> Determination That Delalutin Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. at 36420.

<sup>74</sup> According to § 314.161, the FDA will remove a “drug that the agency determines is withdrawn for safety or effectiveness reasons” from the list of previously approved drugs that are candidates for an Abbreviated New Drug Application. 21 C.F.R. § 314.161 (2003).

<sup>75</sup> *Id.* An Abbreviated New Drug Application does not require preclinical and clinical trial data to establish safety and effectiveness. See also, *Abbreviated New Drug Application*, WIKIPEDIA, [http://en.wikipedia.org/wiki/Abbreviated\\_New\\_Drug\\_Application](http://en.wikipedia.org/wiki/Abbreviated_New_Drug_Application) (last modified Nov. 16, 2012).

<sup>76</sup> Determination That Delalutin Was Not Withdrawn From Sale for Reasons of Safety or Effectiveness, 75 Fed. Reg. at 36421 (indicating Delalutin would remain on the “Discontinued Drug Product List” section of the Orange Book).

<sup>77</sup> *Adeza Submits New Drug Application For Gestiva to Prevent Preterm Births*, DRUGS.COM (May 4, 2006), [http://www.drugs.com/nda/gestiva\\_060504.html](http://www.drugs.com/nda/gestiva_060504.html). Adeza also filed an application for Orphan Drug designation. *Id.*

<sup>78</sup> *FDA Grants Adeza Priority Review for Gestiva to Prevent Preterm Births*, DRUGS.COM (June 5, 2006), [http://www.drugs.com/nda/gestiva\\_060605.html](http://www.drugs.com/nda/gestiva_060605.html). Priority Review “is given to drugs that offer

2006, the FDA Advisory Committee determined that the NICHD data submitted as part of the Gestiva™ application provided sufficient evidence of efficacy and safety to support the approval of Gestiva™ for use in women with a history of preterm delivery.<sup>79</sup> Consistent with the Committee's recommendation, the FDA determined on October 23, 2006 that Gestiva™ would be approved. However, the approval was contingent upon an additional animal study and a few other requirements.<sup>80</sup> On January 31, 2007, Gestiva™ was granted Orphan Drug designation, effectively giving Adeza seven years of market exclusivity so long as the FDA approved the drug.<sup>81</sup>

¶30 After a series of business transactions by which Hologic Inc. ended up with the rights to Gestiva™, KV announced on January 22, 2008 that it had agreed to purchase the rights to Gestiva™ contingent upon FDA approval.<sup>82</sup> The purchase price was \$82 million, with \$7.5 million paid up front and the balance due upon FDA approval.<sup>83</sup> However, on January 26, 2009, KV announced that the FDA was not satisfied with the additional data that had been submitted pursuant to the FDA's Approvable Letter on October 23, 2006.<sup>84</sup> As in 2006, the FDA wanted additional data regarding the efficacy and safety of Gestiva™.<sup>85</sup> Furthermore, the FDA tightened its post-approval trial requirement such that a portion of the study subjects had to be enrolled in the study prior to approval.<sup>86</sup>

¶31 Finally, on February 4, 2011, the FDA approved Makena® (formerly known as Gestiva™) under the FDA's accelerated approval process.<sup>87</sup> Under accelerated approval, the FDA can approve a drug that fills an unmet medical need by determining whether there is a surrogate endpoint benefit that represents a clinically meaningful outcome.<sup>88</sup> In this case, the fulfillment of an unmet need was reducing the risk of delivery before thirty-seven weeks of pregnancy. However, the sponsor of the drug must conduct post-approval trials to demonstrate that the drug in fact does have a clinical benefit, such as improving the outcome of babies born to women treated with Makena®.<sup>89</sup> Currently, KV

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major advances in treatment, or provide a treatment where no adequate therapy exists." *Fast Track, Accelerated Approval and Priority Review*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm> (last updated Aug. 2, 2012).

<sup>79</sup> *FDA Advisory Committee Recommends Approval of Adeza's NDA for Gestiva to Prevent Preterm Birth*, DRUGS.COM (Aug. 29, 2006), [http://www.drugs.com/nda/gestiva\\_060829.html](http://www.drugs.com/nda/gestiva_060829.html).

<sup>80</sup> *Id.*

<sup>81</sup> *Adeza Receives Orphan Drug Designation for Gestiva*, BUSINESSWIRE (Jan. 31, 2007), <http://www.businesswire.com/news/home/20070131005402/en/Adeza-Receives-Orphan-Drug-Designation-Gestiva>.

<sup>82</sup> On April 2, 2007, Adeza was acquired by Cytoc Corp., which then merged with Hologic, Inc. on October 22, 2007. *Hologic Announces Sale of Gestiva*, DRUGS.COM (Jan. 22, 2008), [http://www.drugs.com/nda/gestiva\\_080122.html](http://www.drugs.com/nda/gestiva_080122.html).

<sup>83</sup> *Id.* The purchase price was revised upwards to about \$200 million. *KV Pharma, Hologic change terms of Gestiva sale*, THE SEATTLE TIMES (Jan. 11, 2010), [http://seattletimes.nwsourc.com/html/business/technology/2010765041\\_apuskvpharmagestiva.html](http://seattletimes.nwsourc.com/html/business/technology/2010765041_apuskvpharmagestiva.html).

<sup>84</sup> *KV Pharmaceutical's Launch of Gestiva Delayed*, DRUGS.COM (Jan. 26, 2009), [http://www.drugs.com/nda/gestiva\\_090126.html](http://www.drugs.com/nda/gestiva_090126.html).

<sup>85</sup> *Id.*

<sup>86</sup> *Id.*

<sup>87</sup> *FDA Approves Makena*, DRUGS.COM (Feb. 4, 2011), <http://www.drugs.com/newdrugs/fda-approves-makena-reduce-risk-preterm-birth-risk-pregnant-women-2518.html>.

<sup>88</sup> *Id.*; 21 C.F.R. § 314.510.

<sup>89</sup> The improvements include reducing infant mortality and health problems associated with preterm

is conducting an international trial to confirm the safety and effectiveness of Makena® and will conduct another post-approval infant study that will be completed by 2018.<sup>90</sup>

¶32 Two observations can be drawn from the long history behind Makena®'s approval. First, although the FDA recognized early on that preterm birth was serious enough to accelerate the approval process, the FDA was not completely convinced by the NICHD study. If the FDA had been convinced, then it seems unlikely that the FDA would have delayed approval on two separate occasions, both calling for *additional* data regarding the safety and effectiveness of Makena®. Thus, contrary to public opinion, Makena® is still an unproven drug, which would suggest that it is exactly the type of drug that needs to come under the purview of the FDA.

¶33 Second, even though KV relied on the NICHD study, a taxpayer-funded study, as the basis for its New Drug Application for Makena® (technically, it was a New Drug Application for Gestiva™), KV has had to spend and will continue to spend millions of dollars to comply with the FDA approval process.<sup>91</sup> Thus, contrary to the public outcry that KV is free-riding off the taxpayer dollar, KV is actually spending a lot of money to convince the FDA that Makena® is a safe and effective drug. Moreover, it is easy to forget that by relying on the NICHD study, KV passed on many of the Act's financial incentives that would otherwise have been paid for by taxpayers had KV conducted its own initial studies. In this case, taxpayers saved on having to help KV develop the initial clinical studies. In addition, taxpayers will benefit from the increased tax revenue that otherwise would have been discounted by the fifty percent tax provision of the Act.

#### IV. TO APPROVE OR NOT TO APPROVE?

¶34 According to FDA deputy director Sandra Kweder, the NICHD study showed “higher rates of miscarriages and stillbirths in women taking [Makena®] vs. those taking a placebo, as well as higher rates of pre-eclampsia, deficiencies of amniotic fluid, and gestational diabetes.”<sup>92</sup> In 2006, the FDA's Reproductive Health Drugs Advisory Committee unanimously recommended further studies to investigate the correlation between 17P and second trimester miscarriage and stillbirth.<sup>93</sup> The same panel split thirteen to eight in favor of recommending approval prior to those studies, but even those in favor voiced concerns over the drug's safety and effectiveness.<sup>94</sup> However, for those in favor of an accelerated approval, the potential benefits of treating a “huge and

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delivery *Id.* Failure to find clinical benefit will result in a withdrawal of FDA approval.

<sup>90</sup> *Id.*

<sup>91</sup> *Ther-Rx Corporation Takes Action to Further Ensure High-Risk Women Are Able to Access FDA-Approved Makena™*, KV PHARMACEUTICAL, [http://www.kvph.com/news\\_center\\_article.aspx?articleid=341](http://www.kvph.com/news_center_article.aspx?articleid=341) (last visited Apr. 7, 2013) (claiming that ongoing and scheduled studies are four times larger and twelve times more expensive than the NICHD study).

<sup>92</sup> *FDA's fast-track approval of Makena could backfire on KV*, ST. LOUIS POST-DISPATCH (Mar. 13, 2011, 12:25 AM), [http://www.stltoday.com/business/local/article\\_e4472916-0646-539d-b04a-520756765418.html](http://www.stltoday.com/business/local/article_e4472916-0646-539d-b04a-520756765418.html).

<sup>93</sup> The recommendation was unanimous, twenty-one to zero. *Id.*

<sup>94</sup> *Id.* (“I’m still skeptical,” [said] Dr. Jim Scott, professor and former chair of the Obstetrics and Gynecology department at the University of Utah . . .”).

devastating” problem such as preterm birth outweighed the risks associated with approval.<sup>95</sup>

¶35 The difficulty and reservation (split 13-8) with which the Reproductive Health Drugs Advisory Committee recommended approving Makena indicates that although the effects of a drug may not fully be understood, the medical community is willing, at times, to risk dire consequences, such as stillbirth. At first glance, this seems contrary to the *modus operandi* of the FDA: “to prevent harm to the American people.”<sup>96</sup> But as with almost everything in life, decisions must be made by balancing the risks and rewards of the situation. The key to containing any potential fallout from a decision is to make sure that (1) someone is accountable for the outcomes and (2) as many variables are under direct control as possible. By approving Makena®, the FDA was essentially doing that: (1) bringing the marketing of 17P under its direct purview and (2) making sure that studies on the safety and effectiveness of 17P would be satisfactorily completed.

## V. POST APPROVAL

¶36 After receiving FDA approval for Makena®, KV sent “cease and desist” letters to the various pharmacies that were compounding 17P.<sup>97</sup> Additionally, KV announced that it would be charging \$1,500 per shot of Makena®,<sup>98</sup> which sparked an immediate public outcry since pharmacies had been compounding 17P for \$10 to \$20 per shot over the past few years. On March 30, 2011, the FDA responded to the situation by informing the public that it did not intend to regulate pharmacies that compound 17P from “a valid prescription for an individually identified patient,” unless the compounded drugs were “unsafe, of substandard quality, or [were] not being compounded in accordance with appropriate standards for compounding sterile products.”<sup>99</sup> Soon after, KV reduced the price of Makena® to \$690 per dose.<sup>100</sup>

¶37 On June 15, 2012, the FDA issued a nominal reversal of its prior statement that it would not regulate compounding agencies for 17P.<sup>101</sup> However, the FDA made clear that it would still take into consideration particular patient circumstances to determine whether to regulate the compounding of 17P.<sup>102</sup> Furthermore, the FDA stated that enforcement action for compounded drugs is prioritized using a risk-based approach.<sup>103</sup>

¶38 Although the FDA has recognized that compounded 17P may not pass the rigorous chemical standards required by the Makena® NDA,<sup>104</sup> the FDA’s prior stance on the

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<sup>95</sup> *Id.*

<sup>96</sup> *FDA News Release*, U.S. FOOD AND DRUG ADMIN. (Aug. 6, 2009), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm176119.htm>.

<sup>97</sup> DeNoon, *supra* note 72.

<sup>98</sup> *Id.*

<sup>99</sup> *FDA Statement*, U.S. FOOD AND DRUG ADMIN. (Mar. 30, 2011), <http://www.fda.gov/newsEvents/Newsroom/PressAnnouncements/ucm249025.htm>.

<sup>100</sup> Andrew Zajac, *Drug Maker Lowers Price of Makena Pregnancy Drug to \$690 Per Dose*, L.A. TIMES (Apr. 1, 2011), <http://articles.latimes.com/2011/apr/01/news/la-pn-makena-price-cut-fda-20110401>.

<sup>101</sup> *FDA and CMS Issue Important Updates on Makena®*, KV PHARMACEUTICAL, [http://www.kvph.com/news\\_center\\_article.aspx?articleid=359](http://www.kvph.com/news_center_article.aspx?articleid=359) (last visited Apr. 8, 2013).

<sup>102</sup> *Updated FDA Statement*, U.S. FOOD AND DRUG ADMIN. (June 15, 2012), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm308546.htm>.

<sup>103</sup> *Id.*

<sup>104</sup> *Id.*

regulation of 17P suggests that the FDA may not prioritize the regulation of 17P for two reasons. Firstly, the large price hike makes the drug unaffordable to many patients and thus, gives the FDA a reason to allow the compounding of 17P. Secondly, since 17P has been compounded for several years now, the FDA likely does not see the compounding of 17P as a high-risk situation, despite the long approval history of Makena®. Thus, although the FDA has issued an official reversal of its stance on the regulation of 17P, it does not appear to be a compelling reversal. For that reason, I will assume that the reversal is merely nominal and that the FDA's decision to exercise enforcement discretion is still in effect.

## VI. THE TAKINGS CLAUSE ANALYSIS

¶39 Although the compounding of drugs is illegal under the Federal Food, Drug, and Cosmetic Act (the FDCA), the FDA has historically declined to regulate compounded drugs, leaving primary regulatory responsibility to the states.<sup>105</sup> Since the FDA has not implemented regulations that call for the enforcement of compounded drugs in general, KV would not have a strong argument claiming the illegality under the FDCA of the FDA's decision to exercise enforcement discretion.

¶40 A significantly different, but better, approach can be found in the Takings Clause of the Fifth Amendment. The Takings Clause states that the government cannot take private property for public use without just compensation.<sup>106</sup> Since the FDA did not provide any sort of compensation to KV, the elements of "public use" and "just compensation" do not need be analyzed. Rather, the only element that matters is whether the decision to exercise enforcement discretion constituted a "taking".

¶41 A "taking" can occur in two ways: (1) it can occur through the physical taking of property or (2) it can occur through a government regulation that effectively amounts to a physical taking, but without actually divesting the rights to the property. The FDA's decision to exercise enforcement discretion does not initially appear to fall into either one of these categories. Yet, under further consideration, it seems that the FDA's actions could actually fall under both of these categories.

### A. Physical Taking

¶42 Physical taking is most commonly thought of in the context of real property (i.e. land). However, the Supreme Court has held that the Takings Clause can also be applied to private property other than real property. For example, in *Phillips v. Washington Legal Foundation*, the Court had to address the issue of whether interest income generated from client funds held by an attorney in connection with his practice of law qualified as private property for the purposes of the Fifth Amendment.<sup>107</sup> Prior to 1980, federally insured banks were prohibited from paying interest on demand deposits.<sup>108</sup> But after Congress authorized interest payments in specific instances, forty-eight states

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<sup>105</sup> Boodoo, *supra* note 14, at 231 ("Recognizing the considerable public health benefits and long history of compounding . . . the FDA historically afforded compounding pharmacists an unspoken exemption from the FDCA.").

<sup>106</sup> U.S. CONST. amend. V.

<sup>107</sup> *Phillips v. Wash. Legal Found.*, 524 U.S. 156, 160 (1998).

<sup>108</sup> *Id.*

adopted an Interest on Lawyers Trust Account (“IOLTA”) program. The program mandated that certain client funds had to be deposited into an IOLTA account, with the interest income generated from that account to be paid to foundations that financed legal services for low-income individuals.<sup>109</sup> The legislation was challenged as a taking and the Court subsequently held that the interest income qualified as private property for purposes of the Fifth Amendment.<sup>110</sup>

¶43 A key characteristic of interest income is that it is derived from the principal funds held in a bank account and thus, does not have any value or existence apart from that principal. Yet the Court was willing to expand the concept of private property to include derivatives. Similarly, the value of seven years of market exclusivity under the Act is derived from an orphan drug. Without the rights to market an orphan drug, market exclusivity is meaningless. But since the Court extended the concept of private property to include derivatives, the rights to market exclusivity under the Act should also be treated as property for purposes of the Fifth Amendment. In fact, in a speech before the House of Representatives regarding proposed amendments to the Act, Representative James H. Scheuer expressed the idea that the right to market exclusivity was a property right subject to Fifth Amendment protection.<sup>111</sup>

¶44 If we assume that the right to market exclusivity is protected by the Fifth Amendment, the FDA’s decision to exercise enforcement discretion, effectively usurping that right, can be construed as a direct taking of KV’s private property. Of course, the FDA did not physically take anything from KV, but by refusing to regulate compounding pharmacies, which happens to be the only source of competition for Makena®, the FDA effectively took away the right to market exclusivity.

¶45 A counterargument to this analysis is that the Act guarantees only that the FDA will abstain from approving a generic drug for the same indication for seven years.<sup>112</sup> So technically speaking, the FDA has not violated that rule. However, we should not forget that compounded drugs are still illegal under the FDCA. So if the FDA were to abide by the letter of the law, then it would have to regulate the generic versions of Makena®.

### B. Regulatory Taking

¶46 As discussed in the section above, the right to market exclusivity can be seen as private property for the purposes of Fifth Amendment jurisprudence. With that assumption in place, the FDA’s decision to exercise enforcement discretion can also be seen as a form of regulation that effectively amounts to a taking. As a regulatory body, anything that the FDA does can be construed as a regulation, since any action is essentially an implementation of the laws.

¶47 Under the regulatory takings framework, there are two main approaches by which to analyze the situation. The first one is the *ad hoc* test from *Penn Central Transportation v. New York*, which is essentially a balancing test. The second approach is to determine whether the regulation is a *per se* taking by virtue of depriving the owner

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<sup>109</sup> *Id.*

<sup>110</sup> *Id.* at 172.

<sup>111</sup> 136 CONG. REC. 411, 931 (daily ed. Oct. 23, 1990) (statement of Rep. Scheuer).

<sup>112</sup> 21 U.S.C. § 360cc(a)(2) (2006).



of all economic use of the property.<sup>113</sup> It is difficult to argue that KV has been stripped of all economic use of Makena®, since KV can still sell Makena® in the marketplace. Thus, the most applicable lens by which to analyze the situation is through the *Penn Central ad hoc* test.

¶48 The *Penn Central* test looks at three elements: (1) the character of the government action, (2) the protection of reasonable, investment-backed expectations, and (3) the economic impact of the regulation on the owner.<sup>114</sup> In analyzing the character of the government action, the Court looked to whether the action was taken to protect the public interest<sup>115</sup> and whether the action was discriminatory in nature.<sup>116</sup> In *Keystone Bituminous Coal Ass’n v. DeBenedictis*, the Court found that the restriction on coal mining was in the public interest because the regulation was designed to prevent erosion, which would have caused significant harm to the integrity of the plumbing and structure of neighboring homes.<sup>117</sup> A similar argument could be made that the FDA’s decision to exercise enforcement discretion was in the public interest because it was designed to ensure affordable access to 17P. However, in *Keystone* the Court held that the regulation was not a taking because the protection of the public interest outweighed the economic impact to *Keystone*.<sup>118</sup> More specifically, the Court characterized the economic impact as affecting only two percent of the available coal.<sup>119</sup> However, in our case the economic impact to KV is arguably much more, since doctors do not have an incentive to prescribe Makena® at \$690 per dose when they can prescribe the exact same drug at \$10 to \$20 per dose. Hypothetically then, the FDA’s action potentially usurps 100 percent of the value of Makena®.

¶49 In *Penn Central*, the Court also did not find a taking, holding that on the issue of “character,” the regulation on construction was not discriminatory because the regulation affected all historical landmarks and not just *Penn Central*.<sup>120</sup> However, in our case the FDA’s past decisions to enforce the market exclusivity of other highly profitable drugs, such as hGH, make the FDA’s decision regarding Makena® appear highly discriminatory against KV.

¶50 Secondly, it is clear that KV paid \$200 million for the rights to Makena®<sup>121</sup> under the reasonable expectation that the FDA would enforce market exclusivity. KV was reasonable in its expectation because Congress, the FDA, and even the President all expressed their belief that market exclusivity was a necessary incentive for attracting orphan drug sponsors. Moreover, the FDA’s track record regarding highly profitable

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<sup>113</sup> See *Lucas v. S.C. Coastal Council*, 505 U.S. 1003 (1992) (holding that a regulation barring a land owner from building homes on his beachfront property rendered the property valueless and, thus, the regulation was a per se taking).

<sup>114</sup> *Penn Cent. Transp. Co. v. City of New York*, 438 U.S. 104, 123 (1978) (holding that a New York law restricting the development of historic landmarks, thus preventing *Penn Central* from constructing a 50-story office above the Terminal, was not a taking).

<sup>115</sup> *Keystone Bituminous Coal Ass’n v. DeBenedictis*, 480 U.S. 470 (1987) (holding that it was not a taking to prevent coal mining companies from mining about twenty-seven million tons of coal even though they had purchased the “support estates” that gave them the right to do so).

<sup>116</sup> *Penn Cent. Transp. Co.*, 438 U.S. at 123.

<sup>117</sup> *Keystone Bituminous Coal Ass’n*, 480 U.S. at 485–86.

<sup>118</sup> *Id.* at 502.

<sup>119</sup> *Id.* at 499.

<sup>120</sup> *Penn Cent. Transp. Co.*, 438 U.S. at 135.

<sup>121</sup> *Hologic Announces Sale of Gestiva*, *supra* note 82.

orphan drugs was an additional signal that KV would be able to enjoy exclusive marketing of Makena® for seven years.

¶51 Thirdly, the FDA's decision has had a significant economic impact on KV's ability to survive. KV purchased Makena® as a way to generate cash flow in order to stave off bankruptcy after the FDA shutdown KV's pharmaceutical manufacturing line. If KV did not think that Makena® could generate sufficient cash flow, KV would not have made the purchase. However, in August 2012, KV entered Chapter 11 bankruptcy and cited the FDA's decision to exercise enforcement discretion as a key reason.<sup>122</sup> To make matters worse, KV has already agreed to conduct post-approval trials on Makena® and thus, faces the real risk of sinking hundreds of millions of dollars into an investment that will have a negative return. That is not a good position to be in for a company that is in Chapter 11 bankruptcy.

¶52 In conclusion, the Takings Clause can provide a framework by which KV can argue that the FDA has unlawfully exercised its enforcement discretion.

## VII. CONCLUSION

¶53 The Orphan Drug Act can arguably be deemed a success, if one looks at the number of new drugs that have come on the market for rare diseases compared to the number of drugs that were already on the market for rare diseases prior to the passing of the Act. As we have seen, a large contributing factor to this success was the Amendments to the Act that increased the legal certainty surrounding orphan status. Although this certainty may have come at the cost of being overly inclusive (of drugs that should not be labeled "orphans" because the financial incentive is already there), the history of orphan drugs shows that less than two percent of these orphans have yielded overly large profits. This suggests that the fear of exploitation may not be substantiated. Moreover, the very small probability of very high returns can provide a further incentive, beyond market exclusivity, for firms to make an investment in orphan drugs. Since drug development is a private endeavor and requires reasonable returns on investment, this kind of incentive is arguably good for society.

¶54 Furthermore, all the past signals from Congress, the FDA, and former President George W. Bush, indicate an awareness of the need to provide financial incentives with a willingness to allow some firms to excessively profit from orphan drugs. Subsequently, these signals have set the stage by which firms may come to rely on the fact that the government has tolerated or perhaps even encouraged firms to try to make excessive profits from orphan drugs. The ability to make a large profit from an orphan drug is precisely what motivated KV to purchase Makena®. But as we discussed, KV's reliance on the FDA's past actions, coupled with the large economic impact that the FDA's decision has had on KV's finances, suggest that the government unlawfully took KV's right to market exclusivity of Makena®.

¶55 The risk of exploitation at the cost to consumers is palpable. In fact, it is clear that the original \$1,500 price tag of Makena® would have put the drug out of reach for some qualified individuals, either because one's insurance would not reimburse for the drug or

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<sup>122</sup> *K-V Pharmaceutical Company Files Voluntary Petitions for Reorganization to Restructure Financial Obligations*, KV PHARMACEUTICAL, [http://www.kvph.com/news\\_center\\_article.aspx?articleid=364](http://www.kvph.com/news_center_article.aspx?articleid=364) (last visited Apr. 8, 2011).

because one's deductibles would be too high. But usurping the rights to market exclusivity in the face of precedent is not a legitimate way for the government to limit exploitation. If the FDA is concerned about the exploitation of the Act, then it should write up a report to Congress, imploring them to pass amendments that would limit the rights to market exclusivity. But if past Congressional history can provide any guidance, we should not expect significant change to the Orphan Drug Act. At the same time, it is not in the power of the FDA to enact legislative change. Instead, the FDA should honor its decision to award orphan status to Makena® until the laws dictate otherwise.

