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# OFF-LABEL PRESCRIBING OF SSRIs TO CHILDREN: SHOULD PEDIATRIC TESTING BE REQUIRED, OR ARE THERE OTHER MEANS TO A SAFER END FOR CHILDREN?

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## I. INTRODUCTION

In 2004, the FDA conducted a study investigating suicidal behavior in pediatric patients who were given Selective Serotonin Reuptake Inhibitors<sup>2</sup> (“SSRIs”).<sup>3</sup> The study consisted of a thorough review of published and unpublished controlled clinical trials of antidepressants, and involved nearly 4,400 children and adolescents.<sup>4</sup> The results of the study suggested that suicidal behavior and ideation was twice as likely in children with Major Depressive Disorder (“MDD”) who were prescribed off-label SSRIs.<sup>5</sup> Though the results were statistically insignificant, and thus could have occurred by chance alone, the increase—from 2% in children who received placebos, to 4% in children taking SSRIs—was a 100% increase, proportionally.<sup>6</sup>

Following the study, the FDA directed “the manufacturers of all antidepressant medications to add a ‘black box’ warning that describes the increased risk of suicidality in children and adolescents given antidepressant medications and notes what uses the drug has been approved for in these

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<sup>2</sup> SSRIs are a class of antidepressant medications. Examples of well-known SSRIs, or blockbuster drugs, include Prozac, Paxil, Celexa, Zoloft, and Lexapro.

<sup>3</sup> *Antidepressant Medications for Children and Adolescents: Information for Parents and Caregivers*, NAT'L INST. OF MENTAL HEALTH, <http://www.nimh.nih.gov/health/topics/child-and-adolescent-mental-health/antidepressant-medications-for-children-and-adolescents-information-for-parents-and-caregivers.shtml> (last updated Nov. 22, 2010) [hereinafter *Antidepressant Medications*].

<sup>4</sup> *Id.* Note that, throughout this note, “child” and “children” are used to refer to both young children and to adolescents.

<sup>5</sup> *Id.*

<sup>6</sup> *Id.*

patients . . .” The FDA’s “black box” warning “is the most serious warning placed in the labeling of a prescription medication.”<sup>7</sup> Prescription medications with “black box” warnings also have advertising restrictions.<sup>8</sup>

Despite these warnings, medical doctors continue to prescribe SSRIs and other drugs to treat symptoms and populations not specifically listed on the manufacturers’ labels—i.e., to treat symptoms and populations for which the drug has not received FDA approval.<sup>9</sup> Such “off-label” prescribing is common among physicians; in fact, the American Academy of Pediatrics explicitly approves off-label prescribing:

[I]f based on reasonable medical evidence, if done in good faith in the best interests of the patient, and if done without fraudulent intent, an *unapproved* use of a drug requires only that the same judgment and prudence be exercised in its use as are exercised in medical practice in general for it to conform to accepted professional standards.<sup>10</sup>

In other words, in order to maintain a consistent standard of care, off-label prescribing has to have some scientific basis.<sup>11</sup>

The FDA regulates drug companies to ensure that drugs are safe and effective for use by the patient groups to which the drug company intends to market the drugs; however, the FDA does not regulate—or monitor—doctors.<sup>12</sup> Once a drug is approved for use by one population, or as therapy for a particular ailment, doctors can “vary the conditions of use from those approved in the package insert . . . .”<sup>13</sup> This practice sidesteps the FDA’s safety and efficacy goals and can present risks for patient groups for whom

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<sup>7</sup> *Id.*

<sup>8</sup> Press Release, U.S. Food & Drug Admin., FDA Launches a Multi-Pronged Strategy to Strengthen Safeguards for Children Treated with Antidepressant Medications (Oct. 15, 2004), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2004/ucm108363.htm> [hereinafter Press Release, FDA] (“Advertisements that serve to remind health care professionals of a product’s availability (so-called ‘reminder ads’) are not allowed for products with ‘black box’ warnings.”)

<sup>9</sup> *Id.*

<sup>10</sup> Am. Acad. of Pediatrics Comm. on Drugs, *Unapproved Uses of Approved Drugs: The Physician, the Package Insert, and the Food and Drug Administration*, 98 PEDIATRICS 143, 144 (1996) [hereinafter AAP, *Unapproved Uses*], available at <http://pediatrics.aappublications.org/cgi/reprint/98/1/143>; Russell G. Thornton, *Package Inserts and the Standard of Care*, 16 BAYLOR U. MED. CTR. PROCEEDINGS 502, 503 (2003).

<sup>11</sup> 28 C.J.S. *Drugs and Narcotics* § 22 (2010) (stating that it is the doctor’s “responsibility to be well informed about the [drug] and to base the decision to use it on sound medical evidence”).

<sup>12</sup> AAP, *Unapproved Uses*, *supra* note 10, at 143–44.

<sup>13</sup> Mitchell Oates, *Facilitating Informed Medical Treatment Through Production and Disclosure of Research into Off-Label Uses of Pharmaceuticals*, 80 N.Y.U. L. REV. 1272, 1280 (2005) (quoting Legal Status of Approved Labeling for Prescription Drugs; Prescribing for Uses Unapproved by the Food and Drug Administration, 37 Fed. Reg. 16,503 (Aug. 15, 1972) (codified at 21 C.F.R. pt. 130)).

the medications have not been tested and approved. Nonetheless, off-label prescribing is both widespread and seemingly the only effective means of treating children who require treatment by drugs that have been tested only on adult populations.

It would be ideal if we could give children smaller doses of adult drugs based on weight differences and thereby eliminate the necessity for separate clinical trials, but children cannot be treated as if they are merely “smaller versions” of adult human beings.<sup>14</sup> Children and adults differ physiologically: children do not metabolize drugs in the same way as adults and can experience unpredictable effects when treated with adult medications.<sup>15</sup> In order to avoid dangerously high or inadequately low doses for children, doctors must account for the individual’s pharmacokinetics and pharmacodynamics, both of which are affected by developmental changes in the human body.<sup>16</sup> Improper dosages could create long-term or even permanent developmental effects that are not experienced by adults using the same medications.<sup>17</sup> This creates something of a double bind in the context of MDD and other conditions treated by SSRIs: existing prescription practices are uncertain and may cause significant harm, but the condition may cause significant harm without pharmacological treatment.<sup>18</sup>

Requiring drug companies to conduct clinical studies on children and obtain FDA approval for pediatric use before their drugs are prescribed to children could mitigate many of these potential problems. Drug companies would likely resist this added expense, however, and such clinical studies on children would raise a number of complicated ethical issues. Another alternative is to continue to allow off-label practices, while also requiring doctors to collect data that will enable the FDA to decide which drugs are safe and which drugs merit further pediatric clinical trials.

Using SSRIs as archetypal drugs that have been tested only on adults but are often used to treat children, this Note advocates, first and foremost,

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<sup>14</sup> Carrie Fisher & Thomas G. Keens, *Participation of Children in Research*, 26 WHITTIER L. REV. 823, 831 (2005).

<sup>15</sup> *Id.*

<sup>16</sup> Pharmacokinetics is the way medicines are absorbed and distributed to organs and blood concentration; pharmacodynamics is the way drug receptors mediate how drugs act on the body. ETHICAL CONDUCT OF CLINICAL RESEARCH INVOLVING CHILDREN 68–71 (Marilyn J. Field & Richard E. Behrman eds., 2004).

<sup>17</sup> *See generally Should Children Take Antidepressants?*, HARV. HEALTH PUBL’NS, [http://www.health.harvard.edu/newsweek/Should\\_children\\_take\\_antidepressants.htm](http://www.health.harvard.edu/newsweek/Should_children_take_antidepressants.htm) (discussing how both the risks of medicating and the risks of not medicating are likely to be greatest in the earliest years of life and can have long-lasting effects on a child’s brain development).

<sup>18</sup> *See id.*

for manufacturer-funded clinical trials to examine the safety and efficacy of using adult-approved drugs to treat pediatric populations. When pediatric clinical trials are financially infeasible, however, data collected from prescribing SSRIs off-label to children and adolescents should be compiled, analyzed, and made available as a resource for practitioners, patients, and the FDA.

Compelling drug manufacturers or doctors to cooperate in the process may be difficult. Reforming off-label prescribing practices as they apply to children involves constitutional, statutory, and public policy implications<sup>19</sup> that may conflict with one another. Additionally, a remedial plan, if any is imposed, must consider the interests and perspectives of the parties impacted by the new legal framework: children and parents want the best care available<sup>20</sup> but do not want to shoulder the costs of clinical research; doctors want access to the information necessary to make sound judgments and want the freedom to exercise discretion in treating their patients; FDA-regulated drug companies want to earn profits and want an unobstructed path from their production laboratories to the prescription market; and the government wants to balance the interests of the parties affected by its legislation, but also wants to promote its own interest in protecting social welfare by garnering information on new and existing prescription drugs.

This Note proceeds as follows: Part II provides a basic explanation of the uses and potential side effects of SSRIs as a point of reference to inform the discussion of the legal and policy issues discussed throughout the Note. Part III addresses Congress' constitutional authority to regulate doctors' practices, and attempts to preempt possible constitutional challenges to legislative efforts to issue regulations in this area. Part IV introduces the FDA's existing regulatory framework regarding approval and labeling of new and already-marketed drugs. This Part also addresses the perspectives of proponents and opponents of the existing framework in order to give a clear picture of the competing interests these regulations concern. Part V addresses complications that arise in the application of the FDA's policies to pediatric studies and drug manufacturers. Part VI proposes several potential improvements to the existing laws. This Part emphasizes the value

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<sup>19</sup> These perspectives necessarily overlap. For example, public policy considerations affect statutory interpretation and enter into constitutional analysis, especially where heightened scrutiny is involved.

<sup>20</sup> See, *Wisconsin v. Yoder*, 406 U.S. 205, 242–46 (1972) (Douglas, J. dissenting in part) (citing children's interests as an important factor because "children are entitled to be heard").

of solutions that are compatible with the existing framework and its goals. Part VII concludes.

## II. SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

SSRIs are a class of antidepressant drugs that block the reuptake of serotonin,<sup>21</sup> a neurotransmitter associated with mood and behavior.<sup>22</sup> SSRIs are used to treat Obsessive Compulsive Disorder (“OCD”), non-OCD-related anxiety, Major Depressive Disorder (“MDD”), and other behavioral and cognitive disorders.<sup>23</sup> This class of antidepressants includes drugs with recognizable names, such as Prozac, Paxil, Celexa, Zoloft, and Lexapro.<sup>24</sup> Because most SSRIs are not approved for use by minors, use of SSRIs by this class of patients is, by definition, off-label.<sup>25</sup>

SSRIs have serious potential side effects in child populations. This class of drug can cause increased suicide ideation and suicide itself; this side effect is not limited to those children with MDD.<sup>26</sup> SSRIs can also cause neurological changes; cognitive effects, such as increased agitation; and physical effects, such as tremors.<sup>27</sup> Also, because the juvenile brain has greater plasticity than an adult brain, these harmful side effects may become “locked-in,” rather than dissipating as the child grows older.<sup>28</sup>

Absent a strong potential to substantially benefit children and a lack of safe and effective alternatives, even a small chance of permanent drug-induced symptoms or a minor increase in suicidal behavior and ideation in children is unacceptable. Thus, it is important to note the severity of the symptoms that SSRIs are being used to treat. For example, as the 2004

<sup>21</sup> See *Antidepressant Medications*, *supra* note 3.

<sup>22</sup> See *id.*

<sup>23</sup> Jeffrey A. Bridge et al., *Clinical Response and Risk for Reported Suicidal Ideation and Suicide Attempts in Pediatric Antidepressant Treatment: A Meta-Analysis of Randomized Controlled Trials*, 297 JAMA 1683, 1683–84 (2007), available at <http://jama.ama-assn.org/cgi/reprint/297/15/1683>.

<sup>24</sup> See *Antidepressant Medications*, *supra* note 3.

<sup>25</sup> See *id.* However, Prozac has been approved for treating children: Prozac “is the only medication approved by the FDA for use in treating depression in children ages 8 and older.” *Id.*

<sup>26</sup> While suicides are possible, it is often difficult to ascribe causation. See NAT’L INST. OF MENTAL HEALTH, MENTAL HEALTH MEDICATIONS 6 (2009), <http://www.nimh.nih.gov/health/publications/mental-health-medications/nimh-mental-health-medications.pdf> [hereinafter NIMH, MEDICATION].

<sup>27</sup> *Id.*; see e.g., *Antidepressant Medications*, *supra* note 3 (discussing general problems detected in child patients who are prescribed SSRIs off-label, including suicidal thinking or behavior, nervousness, agitation, irritability, mood instability, or sleeplessness).

<sup>28</sup> Vicki Anderson et al., *Functional Plasticity or Vulnerability After Early Brain Injury?*, 116 PEDIATRICS 1374, 1374–75 (2005), available at <http://pediatrics.aappublications.org/cgi/content/full/116/6/1374>. Plasticity is the brain’s capacity to change. This concept is what enables young children to bounce back from injury. *Id.*

FDA study indicated, 2% of children with MDD experienced suicidal behavior and ideation without taking SSRIs off-label.<sup>29</sup> In addition to suicide risks, individuals with MDD often have difficulty functioning in school, at jobs, and in most basic activities necessary for subsistence.<sup>30</sup> Some extremely depressed patients are almost immobile.<sup>31</sup> In a sense, these patients' lives as functioning persons are nearly gone; they are not dead, but they cannot experience "normal" lives as productive members of society.<sup>32</sup> Accordingly, the goal when treating MDD is to restore "normal" functioning.<sup>33</sup> SSRIs have the potential to help severely afflicted children to achieve this goal, but because hypotheses do not provide enough information about the risks and efficacy of SSRIs on pediatric patients, the estimated benefits of the medicine should be discounted by the likelihood that they could fail to achieve this goal of life-as-functionality.

### III. CONSTITUTIONAL ARGUMENTS FOR AND AGAINST GOVERNMENTAL REGULATION OF OFF-LABEL PRESCRIBING PRACTICES

Congress has authority, under the Commerce Clause, to prevent drugs it considers dangerous to the public from entering interstate commerce.<sup>34</sup> Article I, Section 8 of the United States Constitution states that "Congress shall have power . . . To regulate Commerce . . . among the several States."<sup>35</sup>

Pursuant to this power, Congress enacted the Federal Food, Drug, and Cosmetic Act ("FDCA") to regulate the flow of drugs into interstate commerce. Section 505 of the FDCA provides that no person shall introduce a drug into interstate commerce without FDA approval based on clinical tri-

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<sup>29</sup> See *Antidepressant Medications*, *supra* note 3.

<sup>30</sup> See, e.g., Boadie W. Dunlop & Anne L. Dunlop, Commentary, *Counseling via Analogy: Improving Patient Adherence in Major Depressive Disorder*, 7 J. CLINICAL PSYCHIATRY (PRIMARY CARE COMPANION) 300 (2005), available at <http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=1324962&blobtype=pdf> (citing Kenneth B. Wells et al., *The Functioning and Well-Being of Depressed Patients: Results from the Medical Outcomes Study*, 262 JAMA 914, 914-919 (1989)); *Imaging Identifies Brain Regions and Chemicals Underlying Mood Disorders: May Lead to Better Treatments*, NAT'L INST. MENTAL HEALTH, May 6, 2008, <http://www.nimh.nih.gov/science-news/2008/imaging-identifies-brain-regions-and-chemicals-underlying-mood-disorders-may-lead-to-better-treatments.shtml> [hereinafter *Imaging*].

<sup>31</sup> See *Imaging*, *supra*, note 30.

<sup>32</sup> *Id.*

<sup>33</sup> *Id.*

<sup>34</sup> *Rutherford v. United States*, 442 U.S. 544, 546-47 (1979).

<sup>35</sup> U. S. CONST. art. I, § 8, cl. 3.

als demonstrating the safety and efficacy of the drug.<sup>36</sup> The current version of the FDCA provides that a medication shall not be approved if the Secretary of Health, Education, and Welfare finds: (1) that tests are inadequate<sup>37</sup>; (2) that the results of tests show the medication is unsafe<sup>38</sup>; (3) that there is insufficient evidence to show that the medication is safe<sup>39</sup>; (4) that there is a lack of substantial evidence that the medication will have the effect it purports<sup>40</sup>; or (5) that labeling is false or misleading in any way.<sup>41</sup>

The FDA regulates prescription drugs and biological products that enter the market,<sup>42</sup> but it does not regulate the practice of medicine.<sup>43</sup> Absent state regulation, once the FDA approves a drug, doctors may use their best judgment to prescribe the drug; this includes prescribing the drug “off-label” for purposes and in dosages not expressly approved by the FDA.<sup>44</sup> In other words, “[t]he FDA regulates the marketing and distribution of drugs in the United States, not the practice of medicine, which is the exclusive realm of the individual states.”<sup>45</sup> Furthermore, the FDCA expressly protects off-label use: “Nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or ad-

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<sup>36</sup> Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040 (1938) (codified as amended at 21 U.S.C. § 355 (2006)). (“(a) . . . No person shall introduce or deliver for introduction into interstate commerce any new drug, unless an approval of an application filed pursuant to subsection (b) or (j) is effective with respect to such drug. (b)(1) Any person may file with the Secretary an application with respect to any drug subject to the provisions of subsection (a). Such person shall submit to the Secretary as a part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use. . . .”).

<sup>37</sup> 21 U.S.C. § 355(d)(1) (2006).

<sup>38</sup> *Id.* § 355(d)(2).

<sup>39</sup> *Id.* § 355(d)(4).

<sup>40</sup> *Id.* § 355(d)(5) (“As used in this subsection . . . , the term ‘substantial evidence’ means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.”).

<sup>41</sup> *Id.* § 355(d)(7).

<sup>42</sup> *Abbot ex rel. Abbot v. Am. Cyanamid Co.*, 844 F.2d 1108, 1112 (4th Cir. 1988) (“The FDA’s regulation of prescription drugs and biological products is comprehensive.”).

<sup>43</sup> *United States v. Evers*, 453 F. Supp. 1141, 1148–49 (M.D. Ala. 1978); James M. Beck & Elizabeth D. Azari, *FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions*, 53 *FOOD & DRUG L.J.* (1998).

<sup>44</sup> *E.g.*, *Wash. Legal Found. v. Henney*, 202 F.3d 331, 332–33 (D.C. Cir. 2002); Kasper J. Stoffelmayr, Comment, *Products Liability and “Off-Label” Uses of Prescription Drugs*, 63 *U. CHI. L. REV.* 275, 275–77 (1996).

<sup>45</sup> 28 C.J.S. *Drugs and Narcotics*, *supra* note 11.

minister any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship.”<sup>46</sup>

Thus arises an important question—indeed one that has significant bearing on how off-label prescribing practices can be effectively regulated: “Does [Congress’s] power to exclude from the channels of interstate commerce include the power to control acts performed after interstate commerce is completed?”<sup>47</sup> Assuming for a moment that Congress does have the power to regulate (i.e. place limits upon) *the use* of prescription medications after they have been introduced into interstate commerce, Congress would have the authority to prevent a class of persons (e.g. children) from taking a medication despite the fact that the medication has been approved for use by a different class of persons (e.g. adults). With SSRI’s, this could prevent children from experiencing any harmful, unexplored side effects of the drug, while still allowing adults to enjoy its proven therapeutic benefits.

Today, regulation of the practice of medicine has been left to “the exclusive realm of the individual states.”<sup>48</sup> However, this is not to say that Congress could not regulate some aspects of the practice of medicine if it wanted to. The United States District Court for the District of Columbia noted that Congress’s authority in this area is unsettled: “It appears to be an open question as to whether the FDA could currently regulate this aspect of the practice of medicine [(off-label prescribing)] if it wished to do so.”<sup>49</sup> But more recently, in *Gonzales v. Oregon*, the Supreme Court stated that Congress has the power to regulate the practice of medicine *if it chooses to do so*.<sup>50</sup> In that case, the State of Oregon, physicians, and a group of ill pa-

<sup>46</sup> 21 U.S.C. § 396.

<sup>47</sup> See *United States v. Sullivan*, 332 U.S. 689, 696 (1948). *Sullivan* addressed misbranding medications and a provision in the Federal Food, Drug, and Cosmetic Act of 1938 that prohibited misbranding medications while they are being “held for sale after shipment in interstate commerce.” *Id.* at 333. Addressing the applicable timeline, the Supreme Court stated that a medication is “held for sale in interstate commerce” as long as it is available to consumers: “[T]he language used by Congress broadly and unqualifiedly prohibits misbranding articles held for sale after shipment in interstate commerce, without regard to how long after the shipment the misbranding occurred, how many intrastate sales had intervened, or who had received the articles at the end of the interstate shipment.” *Id.* at 696; see also JESSE H. CHOPER ET AL., *CONSTITUTIONAL LAW* 83 (10th ed. 2006) (citing *Sullivan* as an example of the scope of congressional authority).

<sup>48</sup> 28 C.J.S. *Drugs and Narcotics*, *supra* note 11.

<sup>49</sup> *Washington v. Friedmen*, 13 F. Supp. 2d 51 (D.D.C. 1998), *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999).

<sup>50</sup> *Gonzales v. Oregon*, 546 U.S. 243, 271 (2006) (“Even though regulation of health and safety is ‘primarily, and historically, a matter of local concern,’ there is no question that the Federal Government can set uniform national standards in these areas.” (citation omitted)); see also *Gonzales v. Raich* 545 U.S. 1, 33–34 (2005) (Scalia, J., concurring) (“Although this power ‘to make ... regulation effective’ commonly overlaps with the authority to regulate economic activities that substantially affect interstate



tients challenged the Attorney General's Interpretive Rule that physician-assisted suicide was not a legitimate medical purpose.<sup>51</sup> The Attorney General sought to make it a violation of the Controlled Substances Act to prescribe Schedule II federally controlled medications for the purpose of aiding a patient's suicide.<sup>52</sup> The Court held that the Controlled Substances Act did not empower the U.S. Attorney General to override state law concerning the appropriate use of medications.<sup>53</sup> In so ruling, however, the Court did not dispute the power of the federal government to regulate drugs: "Even though regulation of health and safety is 'primarily, and historically, a matter of local concern,' . . . there is no question that the Federal Government can set uniform national standards in these areas."<sup>54</sup> Thus, whereas the FDCA does not expressly empower the FDA to regulate off-label prescribing, it would appear that Congress has the authority to regulate the practice of medicine if it feels the need to do so.<sup>55</sup> This authority would include the power to regulate off-label prescribing.

#### A. CONSTITUTIONAL RIGHTS OF CHILD PATIENTS

Even if Congress has the authority to regulate off-label prescribing practices,<sup>56</sup> it is possible that constitutional provisions might give children or their parents the right to obtain off-label drugs even in the face of attempts by Congress to limit that right. The Equal Protection Clause of the Fourteenth Amendment is one potential source of these children's rights. The Equal Protection Clause provides that "[n]o State shall . . . deny to any person within its jurisdiction the equal protection of the laws."<sup>57</sup> The Supreme Court has interpreted this clause as a limit on unfairly discriminatory government regulation.<sup>58</sup>

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commerce, and may in some cases have been confused with that authority, the two are distinct. The regulation of an intrastate activity may be essential to a comprehensive regulation of interstate commerce even though the intrastate activity does not itself 'substantially affect' interstate commerce. Moreover, as . . . [*United States v. Lopez*] suggests, Congress may regulate even noneconomic local activity if that regulation is a necessary part of a more general regulation of interstate commerce.")

<sup>51</sup> *Oregon*, 546 U.S. at 252.

<sup>52</sup> *Id.* at 254.

<sup>53</sup> *Id.*

<sup>54</sup> *Id.* at 271 (quoting *Hillsborough County v. Automated Med. Labs., Inc.*, 471 U.S. 707, 719 (1985)).

<sup>55</sup> *Id.*

<sup>56</sup> *Id.*

<sup>57</sup> U.S. CONST. amend. XIV, § 1.

<sup>58</sup> PAUL BREST ET AL., *PROCESS OF CONSTITUTIONAL DECISIONMAKING: CASES AND MATERIALS* 957 (5th ed. 2006).

When government regulations either have a discriminatory impact on a suspect classification (i.e., classifications based on race, alienage or national origin) or infringe upon a fundamental right, courts apply a strict scrutiny analysis.<sup>59</sup> Under strict scrutiny, government regulations will be upheld only if they are narrowly tailored to achieve a compelling state interest and are the least restrictive means of achieving that interest.<sup>60</sup>

Historically, age has not been treated as a suspect classification warranting heightened scrutiny. In *Massachusetts Board of Retirement v. Murgia*,<sup>61</sup> the Supreme Court specifically declined to extend heightened review to differential treatment based on old age:

While the treatment of the aged in this Nation has not been wholly free of discrimination, such persons, unlike, say, those who have been discriminated against on the basis of race or national origin, have not experienced a “history of purposeful unequal treatment” or been subjected to unique disabilities on the basis of stereotyped characteristics not truly indicative of their abilities.<sup>62</sup>

Likewise, unless youth is seen as a significantly different issue, children will not be considered part of a suspect classification entitling them to the benefits of heightened judicial scrutiny.

Children may still receive strict scrutiny if the government regulation burdens a fundamental right, but according to a 2007 case decided by the Court of Appeals for the District of Columbia Circuit, access to prescription drugs probably does not qualify as such a right. In *Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach*,<sup>63</sup> the D.C. Circuit concluded that “there is no fundamental right ‘deeply rooted in this Nation’s history and tradition’ of access to experimental drugs for the terminally ill . . . .”<sup>64</sup> The *Abigail Alliance* plaintiff class comprised competent, terminally ill patients with no alternative government-approved treatment options. These patients claimed they had a constitutional right, protected by the Due Process Clause, to access drugs that had passed FDA

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<sup>59</sup> Cf. *City of Cleburne v. Cleburne Living Ctr.*, 473 U.S. 432, 440–41 (1985) (invalidating a zoning ordinance that restricted a home for the mentally retarded). The Court applied rational basis review to the ordinance. While this case strengthened the use of the rational basis test, the Court did not formally announce a higher standard of review. See generally *id.* This is a continuing problem in equal protection doctrine and theory.

<sup>60</sup> See *City of Boerne v. Flores*, 521 U.S. 507, 546 (1997).

<sup>61</sup> 427 U.S. 307 (1976).

<sup>62</sup> *Id.* at 313.

<sup>63</sup> 495 F.3d 695 (D.C. Cir. 2007) (en banc).

<sup>64</sup> *Id.* at 697.

Phase I trials.<sup>65</sup> The appellate court applied rational basis review,<sup>66</sup> and held that denying terminally ill patients special rights to access experimental drugs was rationally related to the legitimate government goal of protecting these patients from potentially unsafe drugs and unknown side effects.<sup>67</sup> The court placed particular emphasis on the risks associated with drugs that had not been fully tested: “[I]t is unlawful for the Alliance to procure experimental drugs not only because they have not been proven effective, but because they have not been proven safe.” Although the Supreme Court has not yet addressed this particular issue,<sup>68</sup> *Abigail Alliance* supports the notion that the United States Constitution does not give citizens—terminally ill or otherwise—a fundamental right to access drugs that have not been proven safe and effective.<sup>69</sup>

It seems, then, that because age is not a “suspect” classification and there is no fundamental right to unfettered access to potentially unsafe and ineffective drugs, a child’s access to SSRIs would likely be subject to rational basis review.<sup>70</sup> Following the D.C. Circuit’s analysis, the government has a legitimate interest in protecting children from toxicity, suicidal behavior and ideation, and other potentially serious but uncertain side effects of SSRIs, and barring children from accessing these drugs until they are proven safe and effective *for children* is rationally related to that goal. Thus, limiting off-label prescribing of SSRIs and requiring pediatric clinical trials to test the safety and efficacy of these drugs on children would most likely pass rational basis review.

The second possible constitutional challenge to federal regulation of off-label prescribing to children pertains to the children’s parents: if the FDA were to bar children’s off-label access to drugs tested only in adult populations, then it might violate the fundamental right of the parents of the affected children to raise their children in the manner they see fit, subject to

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<sup>65</sup> See *id.* at 698 (explaining that there are three phases of clinical trials a drug must pass for safety and efficacy in order to be approved by the FDA for introduction into the market; Phase I trials consist of a small pilot study of 20 to 80 persons; successful completion of Phase I trials means the drug is sufficiently safe for expanded human trials).

<sup>66</sup> See *Abigail Alliance*, 495 F.3d at 712.

<sup>67</sup> See *id.* at 713. The Supreme Court denied a petition for writ certiorari in January 2008. 522 U.S. 1129 (2008).

<sup>68</sup> *Rutherford* was based on statutory interpretation. See *Rutherford v. United States*, 442 U.S. 544 (1979).

<sup>69</sup> *Abigail Alliance*, 495 F. 3d at 703 (“[I]t is unlawful for the Alliance to procure experimental drugs not only because they have not been proven effective, but because they have not been proven safe.”).

<sup>70</sup> See *City of Cleburne v. Cleburne Living Ctr.*, 473 U.S. 432, 440 (1985).

the constraints of the child's best interests.<sup>71</sup> The Due Process Clause of the Fifth Amendment "provides heightened protection against government interference with certain fundamental rights and liberty interests," including the right to "direct the education and upbringing of one's children."<sup>72</sup> This fundamental right to direct the upbringing of one's child might arguably encompass a parent's right to decide whether or not his or her child should use medications that have been approved by the FDA for adult populations, and prescribed to the child off-label.

Whether FDA regulations infringe upon a parent's Fifth Amendment rights would depend on how broadly courts define a parent's right to make decisions concerning his or her child's upbringing. If interpreted broadly, the FDA regulations may be subject to strict scrutiny, and the government (FDA) would have to demonstrate that the regulations were narrowly tailored to serve its compelling interest.<sup>73</sup> Those interests, which would be the same as those enumerated under the equal protection analysis, would have more difficulty overcoming strict scrutiny's high bar.

Prohibiting pediatric populations from having off-label access to SSRIs might pose serious health risks to patients who have not responded to other available treatments.<sup>74</sup> As a result of the FDA regulations, those patients would not have access to these drugs during the lengthy clinical trials and approval process.<sup>75</sup> Additionally, there are less-restrictive measures, such as government-funded pediatric research concurrent with off-label prescribing, that could potentially address the government's interest in reducing adverse side effects while also minimizing any harm that could

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<sup>71</sup> See *Washington v. Glucksberg*, 521 U.S. 702, 720 (1997); *Wisconsin v. Yoder*, 406 U.S. 205, 214 (1972) (majority) (recognizing a fundamental parental right separate from the Free Exercise Clause of the First Amendment in "the traditional interest of parents with respect to the religious upbringing of their children").

<sup>72</sup> See *Glucksberg*, 521 U.S. at 720; see also *Pierce v. Soc'y of the Sisters of the Holy Names of Jesus & Mary*, 268 U.S. 510, 534 (1925) (recognizing a liberty interest "of parents and guardians to direct the upbringing and education of children").

<sup>73</sup> See *City of Cleburne*, 473 U.S. at 440.

<sup>74</sup> See Press Release, FDA, *supra* note 8 (noting that a new "black box" warning does not prohibit the use of antidepressants with children, but warns prescribers to balance the risk of suicidal thoughts with each patient's needs).

<sup>75</sup> James O'Reilly & Amy Dalal, *Off-Label or Out of Bounds? Prescriber and Marketer Liability for Unapproved Uses of FDA-Approved Drugs*, 12 ANNALS HEALTH L. 295, 304 (2003) ("In 2000, the process for approval was estimated to take between seven to ten years."); Holly Soehnge, *The Drug Price Competition and Patent Term Restoration Act of 1984: Fine-Tuning the Balance Between the Interests of Pioneer and Generic Drug Manufacturers*, 58 FOOD & DRUG L.J. 51, 52 (2003) (estimating that the cost to research, develop, and go through the FDA process is between \$250 to \$600 million for each new drug, and estimating that it takes nine years to test a new drug and obtain FDA approval).

result from a flat ban.<sup>76</sup> Consequently, if parents' right to control their children's upbringing is interpreted to include the right to make key health decisions for their children, an FDA ban on off-label prescribing would arguably fail.

On balance, however, a court confronted with this line of constitutional reasoning is unlikely to reach this conclusion. The FDA is in a better position than parents—and courts—to make decisions about what would benefit children as a group. The FDA regulations on drug manufacturers protect all consumers from the potential harmful effects of experimental drugs by ensuring the safety and efficacy of the drugs introduced into commerce. If this regulatory body concludes that prescribing drugs off-label to children runs too high a risk because of unknown and potentially harmful side effects, the FDA's judgment should trump any parental right or preference. A parent's control over his or her children is subject to the child's best interest<sup>77</sup>; therefore, while parents should have the ultimate decision-making power when it comes to treatment for their children, that power should be limited by what the FDA deems safe and appropriate for all children.

#### IV. STATUTORY AND ADMINISTRATIVE INCENTIVES FOR GENERATING PEDIATRIC STUDIES

"The FDA has taken a carrot-and-stick approach to encourage pediatric studies"<sup>78</sup>; the carrot is a six month exclusivity provision that allows manufacturers of already-approved drugs to receive a patent extension for voluntarily performing FDA-requested pediatric research under the Best Pharmaceuticals for Children Act (BPCA)<sup>79</sup>; the stick is an FDA-imposed requirement that manufacturers of new drugs perform clinical trials for safety and efficacy in child populations in order for certain drugs to receive FDA approval.<sup>80</sup>

<sup>76</sup> A flat ban would not address issues such as increased suicidal thoughts and behaviors in MDD patients who do not respond to other medications and who could possibly be denied effective treatment under a flat ban regime.

<sup>77</sup> See *Washington v. Glucksberg*, 521 U.S. 702, 720 (1997). See also *Wisconsin v. Yoder*, 406 U.S. 205, 214 (1972) (majority) (recognizing a fundamental parental right separate from the Free Exercise Clause of the First Amendment in "the traditional interest of parents with respect to the religious upbringing of their children").

<sup>78</sup> *Drug Research and Children*, FDA.GOV, <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm> (last visited Nov. 18, 2010) (quoting William Rodriguez, M.D., the FDA's science director for pediatrics).

<sup>79</sup> See *id.*

<sup>80</sup> See *id.*

## A. STATUTORY HISTORY

In 1994, the FDA published its final rule (the “1994 Rule”), which “allow[ed] pediatric labeling based on adult studies, when appropriate,” but cautioned that, “in many cases, additional pharmacokinetic and safety data may be needed to support pediatric use statements.”<sup>81</sup> The 1994 Rule required manufacturers that did not provide adequate pediatric research findings to include disclaimers on their labels stating that the drugs had not been tested for safety and efficacy in pediatric populations.<sup>82</sup> Although the FDA did not require pediatric testing, it explicitly expressed its authority to enforce such a requirement in hope of inspiring manufacturers to change a then-current trend of using label disclaimers to avoid pediatric-specific labeling.<sup>83</sup> The FDA’s voluntary approach in 1994 largely failed<sup>84</sup>: “In 1996, only thirty-seven percent of the new molecular entities likely to be used in children had pediatric labels pending approval,”<sup>85</sup> compared to fifty-six percent in 1991.<sup>86</sup>

In reaction to the failure of the 1994 Rule, the FDA took a more insistent approach with its so-called Pediatric Rule a few years later. The new rule sought to allow the FDA to require pediatric testing on already-marketed drugs,<sup>87</sup> and pediatric testing and labeling on new drugs.<sup>88</sup> In certain situations, the Pediatric Rule would have withheld approval of new

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<sup>81</sup> Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of “Pediatric Use” Subsection in the Labeling, 59 Fed. Reg. 64,240, 64,242 (Dec. 13, 1994) (codified at 21 C.F.R. pt. 201).

<sup>82</sup> *See id.*, at 64,240.

<sup>83</sup> *See id.*, at 64,243 (“Although this rule does not add new requirements for conducting pediatric studies, various provisions of the Federal Food, Drug, and Cosmetic Act (the act), the Public Health Service Act (the PHS act), and existing regulations authorize FDA to require such studies under certain circumstances.”).

<sup>84</sup> Lauren Hammer Breslow, *The Best Pharmaceuticals for Children Act of 2002: The Rise of the Voluntary Incentive Structure and Congressional Refusal to Require Pediatric Testing*, 40 HARV. J. ON LEGIS. 133, 153 (2003) (citing Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. 43,902 (proposed Aug. 15, 1997) (codified at 21 C.F.R. pts. 201, 312, 314, 601)).

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

<sup>86</sup> Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,902.

<sup>87</sup> Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,903 (“The rule is also intended to assist in improving pediatric use information for already marketed drugs and biological products where there is a compelling need for more information. The rule would therefore codify FDA’s authority, discussed in the 1994 rule, to require, in compelling circumstances, that manufacturers of already marketed drugs and biological products conduct studies to support pediatric use labeling for the claimed indications.”)

<sup>88</sup> Joanna K. Sax, *Reforming FDA Policy for Pediatric Testing: Challenges and Changes in the Wake of Studies Using Antidepressant Drugs*, 4 IND. HEALTH L. REV. 61, 63 (2007).

drugs until their manufacturers submitted “safety and effectiveness information on relevant pediatric age groups for the claimed indications.”<sup>89</sup> Before this rule was finalized, however, Congress enacted the Food and Drug Administration Modernization Act (FDAMA) in 1997.<sup>90</sup>

#### B. THE FDAMA, THE BPCA, AND THE INTRODUCTION OF EXTENDED-EXCLUSIVITY INCENTIVE FRAMEWORKS

Under the FDAMA, pediatric research was once again voluntary,<sup>91</sup> but the FDAMA included a pediatric exclusivity provision that gave manufacturers a six-month patent extension or exclusivity period in exchange for performing pediatric research.<sup>92</sup> Although Congress hoped that the pediatric research would be accompanied by changes to drug labels to reflect their research findings, the FDAMA allowed manufacturers to benefit from the six-month extension—without making any label changes<sup>93</sup>—as long as they completed the requested testing.<sup>94</sup>

The Best Pharmaceuticals for Children Act (BPCA) of 2002<sup>95</sup> extended the sunset clause of the FDAMA’s exclusivity provision<sup>96</sup> and made at least two significant changes to the incentive structure underlying pediatric research. First, the BPCA made the requested clinical studies less voluntary. Under the amended law, if the FDA determined that a drug required further testing, and the manufacturer elected not to perform that

<sup>89</sup> See Required Pediatric Studies, 21 C.F.R. § 201.23 (2009); Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 62 Fed. Reg. at 43,902; U.S. FOOD & DRUG ADMIN., THE PEDIATRIC EXCLUSIVITY PROVISION: JANUARY 2001 STATUS REPORT TO CONGRESS (2001) [hereinafter PEDIATRIC EXCLUSIVITY PROVISION] available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049915.pdf>; see also, Breslow *supra* note 84, at 161 (discussing the protocol and requirements for applications under the 1998 final rule).

<sup>90</sup> See Breslow *supra* note 84, at 154; Food and Drug Admin. (FDA) Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (codified as amended in scattered sections of 21 U.S.C.).

<sup>91</sup> See Breslow, *supra* note 84, at 154–55.

<sup>92</sup> See Breslow *supra* note 84, at 154; Food and Drug Admin. (FDA) Modernization Act of 1997 § 505A (codified as amended at 21 U.S.C. § 355a(b)(1)).

<sup>93</sup> See *id.*; PEDIATRIC EXCLUSIVITY PROVISION, *supra* note 89, at 25 (noting that members of the pediatric community and brand name manufacturers urged that the additional exclusivity should be tied to labeling changes).

<sup>94</sup> See Breslow, *supra* note 84, at 155.

<sup>95</sup> Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002) (codified as amended at 21 U.S.C. § 355a(n) (2006)).

<sup>96</sup> See *id.* at §8, 115 Stat. at 1414–15; see also AM. ACAD. OF PEDIATRICIANS, PEDIATRIC DRUG TESTING LEGISLATIVE AND REGULATORY HISTORY (2008) [hereinafter AM. ACAD. OF PEDIATRICIANS, PEDIATRIC DRUG TESTING], available at <http://www.aap.org/advocacy/washing/Therapeutics/docs/bpcapreahistory.pdf>.

testing, the FDA could contract a third party to perform the study. In other words, the manufacturer could opt out of the process, but it could not prevent the drug from being tested. The second major revision was to labeling practices. The BCPA gave the FDA explicit authority to request that manufacturers effect specific labeling changes to their drugs. If the manufacturer denied the request, the issue would go before a committee for review,<sup>97</sup> and if the committee agreed with the labeling change and the manufacturer still failed to comply, the FDA could “deem the drug . . . misbranded.”<sup>98</sup>

A year after Congress passed the BPCA, Congress passed the Pediatric Research Equity Act<sup>99</sup> (“PREA”), which codified the 1998 Pediatric Rule<sup>100</sup> and provided the FDA “with additional authority to require pediatric studies of pharmaceutical products when they are needed to ensure their safe and effective use in children.”<sup>101</sup> The PREA requires manufacturers of new drugs to provide data for the FDA “to assess the safety and effectiveness of the drug . . . for the claimed indications in all relevant pediatric subpopulations.”<sup>102</sup> New drugs that are approved as “safe and effective” must also provide dosage instructions for each pediatric subpopulation.<sup>103</sup> Because not all drugs are intended to be used in children, however, a manufacturer can obtain a waiver and forego the pediatric research if it can show that tests on children are impracticable or that the drug would not benefit or be used by children.<sup>104</sup> Drugs that obtain waivers are required to have labels stating that the drug is not safe for children.<sup>105</sup> Similar to the BCPA, the PREA provided that failure to comply with its procedures could result in the drug being deemed “misbranded.” Furthermore, in such cases the drug may be “subject to relevant enforcement action.”<sup>106</sup>

<sup>97</sup> Pub. L. No. 107-109, §8, 115 Stat. 1408, 1413–15 (2002) (“Not later than 90 days after receiving a referral . . . the Pediatric Advisory Subcommittee of the Anti-Infective Drugs Advisory Committee shall . . . review the pediatric study reports[] and make a recommendation to the Commissioner concerning appropriate labeling changes, if any.”).

<sup>98</sup> *See id.* at §3, 115 Stat. at 1410–11.

<sup>99</sup> Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, 117 Stat. 1936 (2003) (codified at 21 U.S.C. 355c (2006)).

<sup>100</sup> AM. ACAD. OF PEDIATRICIANS, PEDIATRIC DRUG TESTING, *supra* note 96.

<sup>101</sup> Press Release, U.S. Dep’t of Health & Human Servs., HHS Statement on Approval of S. 650, the Pediatric Research Equity Act of 2003 (Mar. 21, 2003), <http://www.hhs.gov/news/press/2003pres/20030321b.html>.

<sup>102</sup> Pub. L. No. 108-155, §2, 117 Stat. 1936, 1935–36 (2003) (codified in scattered sections of 21 U.S.C.).

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

<sup>104</sup> *Id.* §2, 117 Stat. at 1937–38.

<sup>105</sup> *Id.* §2, 117 Stat. at 1938.

<sup>106</sup> *Id.* §2, 117 Stat. at 1940.



The PREA and BPCA were amended several times between March and June of 2007,<sup>107</sup> then Congress reauthorized both Acts when it passed the Food and Drug Administration Amendments Act of 2007 (FDAAA)<sup>108</sup> in September 2007.<sup>109</sup> President Barrack Obama's 2010 healthcare legislation added to this framework extended-exclusivity provisions for biological products,<sup>110</sup> but otherwise left this framework intact.<sup>111</sup>

### C. REACTIONS TO THE EXTENDED-EXCLUSIVITY INCENTIVE FRAMEWORK

The FDAMA, BPCA, and PREA built upon one another to form a cohesive framework for regulating new and existing drugs marketed to children. Proponents of the framework claim that the incentive structure helps manufacturers overcome the economic hurdles that often stand in the way of pediatric testing.<sup>112</sup> When the FDAMA first introduced the exclusivity incentive, it measurably bolstered pediatric studies: in the four-year period following the enactment of the FDAMA, in 1997, the FDA granted exclusivity to twenty-eight new products, eighteen of which resulted in label changes to include dosage and safety information.<sup>113</sup> The success these numbers represent stands out in comparison to the lackluster results of the 1994 Rule's entirely voluntary program, under which only eleven studies were completed in seven years.<sup>114</sup> The accomplishments that the framework's incentive structure has inspired in this area are widely recognized:

Indeed, the FDA itself reported that the "pediatric exclusivity provision has done more to generate clinical studies and useful prescribing information for the pediatric population than any other regulatory or legisla-

<sup>107</sup> See AM. ACAD. OF PEDIATRICIANS, PEDIATRIC DRUG TESTING, *supra* note 96.

<sup>108</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007).

<sup>109</sup> See AM. ACAD. OF PEDIATRICIANS, PEDIATRIC DRUG TESTING, *supra* note 96.

<sup>110</sup> 2 U.S.C.A. § 262(i)(1) ("The term 'biological product' means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.")

<sup>111</sup> The "biological product" exclusivity provisions essentially mirror those provisions for drugs: if the FDA determines that information relating to the use of a medication, new or already on the market, has potential to produce health benefits for pediatric patients, the Secretary may request that the manufacturer of the drug perform pediatric tests. Compliance with FDA-requested pediatric testing increases the manufacturer's market exclusivity periods by six months: from four years to four years and six months and from twelve years to twelve years and six months. See Pub. L. No. 111-148, §7002, 124 Stat. 119, 819-21 (2010).

<sup>112</sup> See Sax, *supra* note 88, at 79.

<sup>113</sup> See Breslow, *supra* note 84, at 163.

<sup>114</sup> *Id.*

tive process to date.” Even pharmaceutical groups commended the legislation for inspiring them to undertake the complicated task of pediatric clinical research, admitting that prior federal regulations had done little to accomplish this end.<sup>115</sup>

Additionally, manufacturers highlight the successes of the current pediatric exclusivity provision,<sup>116</sup> and point out the FDA’s recent success reports:

As of Feb. 20, 2009, labeling changes have been made to more than 260 products that were studied in children under BPCA or PREA. Of the more than 170 drugs studied just under the exclusivity incentive program within the BPCA, 159 have new pediatric labeling information including: 45 drugs with new or enhanced pediatric safety data that [had not] been known before[;] 27 drugs with new dosing or dosing changes[; and] 50 drugs with information stating that they were not found to be effective in children.<sup>117</sup>

Still, despite its significant headway and general support from pharmaceutical companies, opponents of the framework’s incentive structure feel that an incentives-only approach does not go far enough; they claim that the FDA should affirmatively require pediatric research in “appropriate cases,”<sup>118</sup> such as when an existing drug is part of a smaller, less competitive market in which extended exclusivity is an inadequate incentive.<sup>119</sup> Additionally, some argue that the incentive structure under the framework is also inadequate because it permits manufacturers to benefit from the six-month extended-exclusivity provision whether or not the drug is safe for children and whether or not the manufacturer changes its labels; the

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<sup>115</sup> *Id.* (quoting Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research before the Senate Committee on Health, Education, Labor, and Pensions, on May 8, 2001). Doctor Woodcock’s testimony is available at <http://www.fda.gov/NewsEvents/Testimony/ucm115220.htm>.

<sup>116</sup> *See* Breslow, *supra* note 84, at 163. (Dr. Robert Ward noted that in the three years following the enactment of the FDAMA, eighteen of twenty-eight products granted exclusivity contained “new dosage, safety, or adverse event-reporting information” as compared to only eleven pediatric research studies completed over the course of the previous seven years.).

<sup>117</sup> U.S. Food & Drug Admin., *Should Your Child Be in a Clinical Trial?*, CONSUMER UPDATE, Feb. 27, 2009, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048699.htm>.

<sup>118</sup> H.R. Rep. No. 107-277, at 56 (2001). The opponents were members of the House of Representatives Committee on Energy and Commerce who dissented from the committee recommendation that the BPCA pass. These members included John D. Dingell, Sherrod Brown, Henry A. Waxman, Peter Deutsch, Frank Pallone, Jr., Tom Barrett and Bart Stupak. *Id.* at 58.

<sup>119</sup> *See id.* at 57. The Secretary’s only responsibility in accepting or rejecting the reports [of pediatric research qualifying for the six-month exclusivity] shall be to determine . . . whether the studies fairly responded to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing.

framework requires only that the manufacturers report their results to the FDA.<sup>120</sup>

The harshest criticisms of the framework target the extreme profits drug manufacturers stand to gain through the six-month exclusivity provision.<sup>121</sup> These attacks are not without merit: under the six-month extension, some drug manufacturers earned profits several hundred times the costs of their pediatric research<sup>122</sup>—research that critics feel manufacturers should be responsible for without any economic incentive at all. Critics allege that, even after realizing excessive profits from their research efforts, manufacturers will likely raise drug prices in order to pass on some of the increased costs of pediatric research to customers.<sup>123</sup> The exclusivity provision makes this relatively easy to do because it delays the introduction of lower-priced generic drugs into the market.<sup>124</sup> In 2001, the FDA estimated that the exclusivity periods could cost consumers an extra \$13.9 billion over a twenty-year period.<sup>125</sup>

Proponents are quick to rebut criticisms of the framework's incentive structure.<sup>126</sup> To those who focus on the legislation's effectiveness in producing important medical information, the profits to drug companies do not rival the benefits to children's health, which does not have a price tag.<sup>127</sup> As explained by Dr. Robert Ward, a practicing pediatrician and member of the American Academy of Pediatricians (AAP), the primary beneficiaries are doctors and patients: "the greatest windfall has been in the area of pediatric research and information now available for pediatricians . . . . Dollars and cents arguments can not [sic] adequately provide the evidence of the effec-

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<sup>120</sup> See PEDIATRIC EXCLUSIVITY PROVISION, *supra* note 89, at 24–25.

<sup>121</sup> See Breslow, *supra* note 84, at 167.

<sup>122</sup> Estimates of added costs of pediatric safety and efficacy research varied from \$1 million to \$7 million in an estimate by the National Institute of Child Health and Human Development estimate to \$5 million to \$35 million in an estimate by the Pharmaceutical Research and Manufacturers of America. *See id.* Contrast those numbers with the additional revenues due to the grant of exclusivity, *see* PEDIATRIC EXCLUSIVITY PROVISION, *supra* note 89, at 14, of \$975 million (for Claritin) and \$831 million (for Prozac), *see id.* at 168, and it is easy to see why opponents are outraged. For the heartburn medication Prilosec, the pediatric clinical study cost between \$2 and \$4 million, but the drug company reaped a 36,000% return on its investment, earning \$1.4 billion over the course of its six-month extension. *See id.*

<sup>123</sup> *See id.* at 134. The manufacturers are not likely to recoup *all* the costs via price increases, because a rise in prices will result in a decrease in demand.

<sup>124</sup> See PEDIATRIC EXCLUSIVITY PROVISION, *supra* note 89, at 14.

<sup>125</sup> *See id.* This estimate was provided by the FDA, although it is unclear how the estimate was calculated.

<sup>126</sup> *See id.*

<sup>127</sup> See Breslow, *supra* note 84, at 163.

tiveness or importance of this program.”<sup>128</sup> In fact, researchers and health-care providers in pediatric oncology have argued that the incentives created under the framework are insufficient, and that longer exclusivity provisions are necessary to support voluntary manufacturer research on cancer drugs in pediatric populations.<sup>129</sup>

Furthermore, not all drug companies realize inordinate gains. Dr. Richard Gorman, a practicing pediatrician for twenty-nine years and chair of the AAP section on Clinical Pharmacology and Therapeutics,<sup>130</sup> stated that the returns from the exclusivity provision enjoyed by companies responding to FDA research requests have not been excessive.<sup>131</sup> In support of his view, Dr. Gorman cited a 2007 study from the *Journal of the American Medical Association* that concluded that “[t]he median annual sales of a drug receiving pediatric exclusivity were \$180 million[,] with a return on investment of 1.5 times the cost of the study.”<sup>132</sup>

By increasing the amount of information available about prescription drugs, and by easing consumer access to that information, the framework also addresses other concerns about the incentive structure. The FDA is required to publicize the results of pediatric studies performed pursuant to the framework.<sup>133</sup> So, although drug companies may benefit from the extended-exclusivity provision even if their research shows that their drugs are not safe for pediatric use, the results of the studies become public information that is likely to prevent doctors from prescribing the drugs to children, and manufacturers from marketing their drugs to pediatric use.<sup>134</sup> It is also

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<sup>128</sup> *Id.*

<sup>129</sup> See PEDIATRIC EXCLUSIVITY PROVISION, *supra* note 89, at 24.

<sup>130</sup> *Ensuring Safe Medicines and Medical Devices for Children: Hearings Before Senate Health, Education, Labor, and Pensions Comm.*, 110th Cong. (2007) (testimony of Richard L. Gorman) available at <http://www.aap.org/advocacy/washing/Testimonies-Statements-Petitions/03-27-07-Gorman.pdf>.

<sup>131</sup> See *id.*

<sup>132</sup> *Id.*

<sup>133</sup> See 21 U.S.C. at §502(j) (2006).

<sup>134</sup> See Letter from Henry A. Waxman, Chairman, Comm. on Oversight & Gov't Reform, to Andrew C. von Eschenbach, Commissioner, U.S. Food & Drug Admin. 8–11 (Nov. 7, 2007), available at <http://oversight.house.gov/documents/20071130102744.pdf> (posting examples of negative press received by drug companies). Drug companies cannot market their products to off-label patient groups; however they can report anecdotal information and theoretical considerations about off-label uses to physicians. *Id.* at 1; U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: GOOD REPRINT PRACTICES FOR THE DISTRIBUTION OF MEDICAL JOURNAL ARTICLES AND MEDICAL OR SCIENTIFIC REFERENCE PUBLICATIONS ON UNAPPROVED NEW USES OF APPROVED DRUGS AND APPROVED OR CLEARED MEDICAL DEVICES (2009), available at <http://www.fda.gov/oc/op/goodreprint.html> (Manufacturers are not allowed to market their drugs for unapproved uses and patient groups; however, they can disseminate “medical journal articles and medical or scientific reference publications on unapproved uses of drugs and . . . medical devices.”).

worth noting how ineffective the incentive framework would be if exclusivity were conditioned on proof of safety and efficacy. Such a framework would encourage manufacturers to falsify positive results for dangerous drugs; or, alternatively, it could completely quell the financial incentives as manufacturers discount their potential gains by the possibility of their research going uncompensated.

Additionally, regardless of the size and competitiveness of a particular drug market, drugs that the FDA deems to require more testing will likely be tested even if the exclusivity provisions provide an inadequate financial incentive.<sup>135</sup> If manufacturers choose to forego the research, the FDA will contract it to third parties.<sup>136</sup> Thus, as long as there are tax dollars available to fund third-party research, manufacturers cannot escape harmful research findings, and drugs that are unsafe or ineffective for use by pediatric populations will be labeled as such no matter who performs the study.<sup>137</sup>

## V. PUBLIC POLICY AND ADDITIONAL PRACTICAL COMPLICATIONS

Beginning with the FDAMA in 1998, healthcare legislation has made great strides toward garnering information on new and already-marketed drugs that are prescribed to, but not intended for, pediatric patients. Even with these laws firmly in place, however, a number of problems arise when the framework is applied. The ethical issues of using children as research subjects presents one of these problems; another problem emerges when the FDA attempts to cajole drug companies into cooperating with its mandates.

### A. CHILDREN: THE RISK–BENEFIT PROFILE OF CLINICAL RESEARCH

Some child research is considered too dangerous to perform. In some cases this is not because of the danger of the drug itself, but because treatment must be denied to the control group.<sup>138</sup> Randomized clinical trials are “generally considered the best method for determining whether an experimental measure should enter the realm of accepted therapy.”<sup>139</sup> Rando-

<sup>135</sup> See *supra*, Part IV(B), discussing the FDA’s ability to require testing.

<sup>136</sup> See 42 U.S.C. § 284m(b) (2006).

<sup>137</sup> See 21 U.S.C. §355a (j)–(k).

<sup>138</sup> See e.g., *Prozac Is Risky for Children Too*, BBC NEWS, Dec. 10, 2004, <http://news.bbc.co.uk/2/hi/health/4083545.stm> (stating that although using anti-depressant medications can increase suicidal behavior in children, untreated MDD is more likely to result in actual suicide).

<sup>139</sup> MICHAEL H. SHAPIRO ET AL., *BIOETHICS AND LAW, CASES, MATERIALS AND PROBLEMS* 257 (2nd ed. 2003).

mized clinical trials consist of randomly assigning participants to one of two or more study groups, exposing one group to the experimental condition (the drug being tested) and the other group to a standard approach (the standard treatment or a placebo, which means giving no real treatment at all).<sup>140</sup> Critics oppose the use of placebos when reasonably effective treatments exist, especially when the condition being studied places the participants at risk of serious harm or death without the use of available medications.<sup>141</sup> These critics contend that depriving the patient-participant of a much-needed drug subjects the control group to an unreasonable risk in order to satisfy an unduly demanding scientific standard.<sup>142</sup>

Conversely, defenders of using placebo control groups claim that placebos help ensure the accuracy of scientific findings and are ethical so long as participants give informed consent to the possibility of being placed in a placebo group.<sup>143</sup> In the case of childhood depression, being placed in a placebo group may lead to a substantial risk of serious harm, including increased suicidal ideation and other behaviors associated with not treating the disorder.<sup>144</sup> However, not creating a placebo group could compromise the quality of the research results, possibly foreclosing FDA approval and eliminating the potential benefits to all pediatric patients.

While clinical trials are crucial in identifying which drugs are safe and effective for use by children, those children not involved in a given study will not have access to the drug throughout the duration of the study unless some level of off-label prescribing is allowed. This is important given that many off-label SSRIs, and other drugs commonly used by pediatric populations, would no longer be available to those not involved in the study.

Other clinical studies on children may be too dangerous because of the drug involved. In these cases, child research does not happen either because an Institutional Review Board finds the benefits to children to be too insubstantial in light of the potential harms and refuses to let the studies go forward,<sup>145</sup> or because manufacturers refuse to perform the research for fear

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<sup>140</sup> *See id.*

<sup>141</sup> *See id.* at 259.

<sup>142</sup> *See id.*

<sup>143</sup> *See id.* (Risks from being placed in the placebo arm due to the untreated disorder must not be substantial.)

<sup>144</sup> *See Prozac Is Risky for Children Too*, *supra* note 138 (stating that “when people with depression are left untreated, 15% will actually commit suicide”).

<sup>145</sup> HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject, or by a monitoring procedure that is likely to contribute to the subject’s well-being,

of tort suits from research participants.<sup>146</sup> Critics of permissive standards for off-label prescribing may favor prohibiting off-label prescribing in these types of cases, arguing that if clinical trials are too dangerous to perform, then off-label prescribing must also be too dangerous. However, because the drugs in question have not been tested for safety and efficacy in pediatric populations, it is difficult—if not impossible—to know in advance which drugs pose a danger to children.

Alternatively, some may argue that if a drug is safe for clinical trials, then it should also be considered safe for off-label prescribing. This argument, as with the converse for drugs deemed too dangerous, does not hold up. Not only does this completely obviate the need for clinical trials, it also overlooks that a risk that may be justified by the information it can generate in a methodologically sound clinical trial but may not be justified without a methodical information-gathering objective. That is, general off-label use imposes risks without the direct benefits of sound clinical trials.

### 1. SSRI Research on Children

To illustrate the complicated nature of clinical trials involving child patients, consider how such trials would be conducted for SSRIs. In addition to the general risk–benefit challenges discussed above, drug research involving children and adolescents also raises numerous challenges on account of the age of the clinical subject. For example, a child’s brain is more malleable than an adult’s brain, and this exposes children to the risk that any damage done to them as a result of a study could affect them for years to come.<sup>147</sup> Similar to the way stepping on a young tree would alter its

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only if the IRB finds that: (a) The risk is justified by the anticipated benefit to the subjects; (b) The relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches; and (c) Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians, as set forth in §46.408.”); *see also*, Shapiro et al., *supra* note 139, at 208–12 (Institutional Review Boards approve research studies based on several factors such as a determination that risks to subjects are minimized and that such “[r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result”); 45 C.F.R. 46.405 (2009).

<sup>146</sup> *See* Breslow, *supra* note 84, at 140–41.

<sup>147</sup> *See* Christopher C. Gize & Mayumi L. Prins, *Is Being Plastic Fantastic? Mechanisms of Altered Plasticity After Developmental Traumatic Brain Injury*, 28 DEVELOPMENTAL NEUROSCIENCE 364, 366–67 (2006), available at [http://faculty.neuroscience.ucla.edu/institution/publication-download?publication\\_id=212761](http://faculty.neuroscience.ucla.edu/institution/publication-download?publication_id=212761) (noting that while subjects can get back to their pre-injury baselines of functionality, the baselines of their peers will have already moved on).

growth, causing harm to young children could irreversibly alter the rate or nature of their future development.<sup>148</sup>

The more common problems posed by the scientific method are also present in studies of SSRIs. As with all clinical studies, “control groups” are a necessary part of experimental design for SSRI studies because they serve as a baseline against which researchers can measure the effects of a therapeutic “test” treatment.<sup>149</sup> In these studies, placebo groups are control groups that are given sugar pills or other inert pills in place of the drug being tested.<sup>150</sup> For studies involving pediatric MDD patients and SSRIs, using control groups may pose ethical problems.<sup>151</sup> Because these studies necessarily require that the variable being tested (the SSRI) be the only thing varied between the two groups,<sup>152</sup> the control group is often denied not only SSRIs, but also psychotherapy and other known forms of treatment.<sup>153</sup> This puts the control group at risk. As discussed in greater detail above,<sup>154</sup> a small percentage of children with MDD experienced suicidal behavior and ideation when the condition goes untreated.<sup>155</sup> Children with untreated MDD also have difficulty functioning in their every-day lives. Thus, clinical trials of SSRIs on children with MDD run the serious risk of leaving child patients in the control group exposed to the dangers of untreated MDD.<sup>156</sup>

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<sup>148</sup> See generally Leonard H. Glantz, *The Law of Human Experimentation with Children*, in CHILDREN AS RESEARCH SUBJECTS: SCIENCE, ETHICS, AND LAW 103, 103–28 (Michael A. Grodin & Leonard H. Glantz eds., 1994) (providing a historical overview of pediatric testing).

<sup>149</sup> See, e.g., NEIL A. CAMPBELL & JANE B. REECE, *BIOLOGY*, 18 (6th ed. 2002).

<sup>150</sup> See, e.g., Merriam-Webster’s Medical Online Dictionary, <http://www.merriam-webster.com/medical/control> (last visited March 12, 2009) (defining control as “an experiment in which the subjects are treated as in a parallel experiment except for omission of the procedure or agent under test and which is used as a standard of comparison in judging experimental effects”); see also CAMPBELL & REECE, *supra* note 149.

<sup>151</sup> SHAPIRO ET AL., *supra* note 139.

<sup>152</sup> To ensure that any changes recorded are due to the effects of the single known variable, and not some unaccounted for variable.

<sup>153</sup> See *id.*

<sup>154</sup> See *supra* Part II.

<sup>155</sup> See *supra* Part I, discussing the results of the FDA’s study of antidepressants on children with MDD.

<sup>156</sup> *Prozac Is Risky for Children Too*, *supra* note 138 (noting that while the use of anti-depressants can increase the risk of suicidal behavior in children, there have been no reported deaths, whereas as many as 15% of people with untreated depression will actually commit suicide); The increase in suicidal ideation and behavior reported by the FDA in 2004, *supra* note 3, reflects an increase while using SSRIs as compared to other forms of treatment for MDD and related disorders. It is not the purpose of this paper to claim that SSRIs cause suicide, rather there are risks associated with the drugs—such as suicidal thoughts and behavior—that we know little about because of the absence of testing the medications on children.



B. DRUG COMPANIES COMPROMISE INFORMED CONSENT BY  
WITHHOLDING INFORMATION ON SAFETY AND EFFICACY

Lack of informed consent is a potential problem area in the off-label use of drugs. Often, patients know only what their doctors tell them about the medications they are prescribed off-label. Doctors, in turn, are informed by the available literature regarding a particular drug and by their hands-on investigations of that drug. Thus, if a doctor's knowledge is to some extent constrained by the amount of literature available, and that doctor's knowledge also represents the upper limit of what a patient could know, then the amount of literature generated regarding a particular drug could have a significant bearing on the doctor-patient relationship. In other words, if the doctor does not know of all of a drug's potential side effects, then the patient will not either.

Some consumer advocacy groups have accused drug companies of withholding safety and efficacy information concerning SSRIs.<sup>157</sup> Certain drug companies<sup>158</sup> have refused to disclose the details of several clinical trials involving depression in pediatric populations.<sup>159</sup> Drug companies claim that the findings of these studies are trade secrets paid for with private company funds, and thus are private property.<sup>160</sup> Whether this practice is legal or not,<sup>161</sup> drug manufacturers that withhold data distort the completeness of the available information, which in turn disables fully informed consent on the part of the patients using these drugs.<sup>162</sup>

A report by the United States Senate Committee on Finance charged that, in addition to blatantly withholding harmful clinical-study results, GlaxoSmithKline (GSK) manipulated its research with respect to Paxil, one of its anti-depressants.<sup>163</sup> This was accomplished by placing research participants who had previously attempted suicide into the placebo group in

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<sup>157</sup> See Shankar Vedantam, *Antidepressant Makers Withhold Data on Children*, WASH. POST, Jan. 29, 2004 at A01.

<sup>158</sup> Such as the makers of Paxil, Zoloft, and Effexor. *Id.*

<sup>159</sup> *See id.*

<sup>160</sup> *See id.*

<sup>161</sup> *See id.* (claiming it is legal to suppress unfavorable clinical-trial results, but this practice distorts the scientific record).

<sup>162</sup> If it is "legal," new legislation could be passed altering trade secret laws to require drug companies to disgorge such information.

<sup>163</sup> See Letter from Iowa Senator Chuck Grassley, Ranking Member, Senate Comm. on Finance, to Christopher Viehbacher, President, U.S. Pharmaceuticals GlaxoSmithKline 4 (Feb. 6, 2008), available at <http://finance.senate.gov/press/Gpress/2008/prg061208.pdf>.

order to make it appear as if those in the Paxil group experienced comparatively fewer incidents of suicidal thoughts and behavior.<sup>164</sup>

In 2007, lawmakers responded to concerns over companies withholding their privately funded clinical-trial results by passing the Food and Drug Administration Amendments Act of 2007<sup>165</sup> (FDAAA). “The law requires mandatory registration and results reporting for certain clinical trials of drugs, biologics, and devices.”<sup>166</sup> Title VIII of the FDAAA “requires all clinical trials of drugs, biologics, and devices, except for Phase I clinical trials, to be registered in the clinical trial registry databank. . . . This requirement is a significant change from prior law, which only required registration of trials for serious or life-threatening diseases.”<sup>167</sup> The FDAAA requires the FDA to publish results of clinical trials that boast efficacy claims or those conducted after a drug is approved, along with patient sample demographics and secondary outcomes.<sup>168</sup>

The FDAAA provides for civil penalties of up to \$10,000 per day for failure to comply with registration requirements, and allows for additional penalties for failure to correct such violations within thirty days.<sup>169</sup> Additionally, the bill provides for up to \$1,000,000 in civil penalties for knowingly making false statements; misrepresenting a material fact; or failing to disclose a material fact relating to any drug subject to an abbreviated drug application.<sup>170</sup> Even more importantly, Iowa Senator Chuck Grassley is seeking legislation that would call for criminal penalties for drug compa-

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<sup>164</sup> See Letter from Iowa Senator Chuck Grassley, Ranking Member, Senate Comm. on Finance, to Christopher Viehbacher, President, U.S. Pharmaceuticals GlaxoSmithKline 4 (Feb. 6, 2008), available at <http://finance.senate.gov/press/Gpress/2008/prg061208.pdf>. This information was divulged in a report by Dr. Joseph Glenmullen, a professor of psychiatry at Harvard University, based on a review of documents uncovered in litigation. See *id.* at 3. Dr. Glenmullen provided expert witness testimony in several lawsuits, pending at the time of the Senate Committee Report, which concluded that GSK “knew for almost two decades that Paxil is associated with an increased risk of suicide.” *Id.* See Jim Giles, *Did GSK Trial Data Mask Paxil Suicide Risk?* PAROXETINE.COM (Feb. 8, 2008), [http://www.paroxetine.com/news\\_article.html?tx\\_ttnews%5Btt\\_news%5D=1312&tx\\_ttnews%5BbackPid%5D=69&cHash=3a64e76a22](http://www.paroxetine.com/news_article.html?tx_ttnews%5Btt_news%5D=1312&tx_ttnews%5BbackPid%5D=69&cHash=3a64e76a22).

<sup>165</sup> Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, 121 Stat. 823 (2007).

<sup>166</sup> See ClinicalTrials.gov, Investigator Instructions, <http://www.clinicaltrials.gov/ct2/invest> (last visited March 12, 2009).

<sup>167</sup> Cary C. Messplay & Sarah E. Burrell, *Implications of FDAA 2007: Changes are afoot following the FDA's reauthorization*, CONTRACT PHARMA, Nov.–Dec. 2007, at 18, available at [http://www.hunton.com/files/tbl\\_s47Details%5CFileUpload265%5C2117%5CContractPharma\\_Messplay-Burrell\\_Nov-Dec\\_2007.pdf](http://www.hunton.com/files/tbl_s47Details%5CFileUpload265%5C2117%5CContractPharma_Messplay-Burrell_Nov-Dec_2007.pdf).

<sup>168</sup> See *id.*

<sup>169</sup> See *id.*

<sup>170</sup> See Food and Drug Administration Amendments Act of 2007, § 902(b).

nies that “manipulate or withhold data to hide or minimize findings about safety and/or efficacy, . . . [thereby putting] patient safety at risk.”<sup>171</sup> Senator Grassley is also “working on legislation that would require that companies certify to the FDA that they gave the FDA complete and accurate data related to the safety and efficacy of their products and that the information is not false or misleading.”<sup>172</sup>

Drug companies have additional concerns unrelated to regulation. Drug manufacturers have to contend with tort liability from lawsuits brought on behalf of patients harmed in both clinical and patient settings. In deciding whether to test a drug on pediatric populations, manufacturers also have to consider ethical dilemmas in child research as well as a risk that the research could result in lower profits if the drugs prove to be unsafe or ineffective for pediatric populations.

## VI. POSSIBLE SOLUTIONS

It may not be possible to legislate-away all of the potential problems with the existing FDA framework. Withholding treatment from children in “control groups” will always pose ethical concerns, as will using children as test subjects for potentially unsafe drugs. Similarly, drug companies, like all successful companies, will always oppose federally enacted requirements that are adverse to their business interests. Thus, improvements to the existing framework should not try to change those things that are beyond the legislature’s control; rather, they should focus on ways to work around potential problem areas. In the areas of research funding and data collection, such solutions are possible—and compatible—with the existing framework.

### A. BPCA INCENTIVE STRUCTURES DESIGNED TO DRIVE RESEARCH

Although some have criticized the incentive structure of the FDAMA, BCPA, and PREA framework for granting exclusivity extensions even when a drug proves not to be safe and effective for children, as previously discussed, the structure would hardly be effective if the exclusivity period

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<sup>171</sup> Grassley, *supra* note 164. Recently, Eli Lilly pled guilty to a charge of illegally promoting off-label uses of its drug Zyprexa. Eli Lilly agreed to pay \$1.415 billion to resolve the allegations, including a \$515 million criminal fine, the largest “the largest ever in a health care case, and the largest criminal fine for an individual corporation ever imposed in a United States criminal prosecution of any kind”. Press Release, U.S. Dep’t of Justice, Eli Lilly and Company Agrees to Pay \$1.415 Billion to Resolve Allegations of Off-label Promotion of Zyprexa (Jan. 15, 2009), available at <http://www.usdoj.gov/opa/pr/2009/January/09-civ-038.html>.

<sup>172</sup> Press Release, U.S. Dep’t of Justice, *supra* note 171.

were extended only upon a finding of safety and efficacy. Such a contingency could quash manufacturer participation altogether, or it could lead to falsified results. Still, the existing framework could be improved in a number of ways: one possible improvement is to alter the incentive structure to reimburse manufacturers when their drugs prove not to be safe and effective in child populations, and extend exclusivity only to those manufacturers that produce safe and effective drugs. Advocates of this so-called Waxman/Brown Substitute claim that it would replace “the six-month exclusivity incentive with direct reimbursement of the costs of the studies, plus a 100 percent profit.”<sup>173</sup> Though this provides less of a research incentive than a guaranteed exclusivity extension, it may also provide a workable middle ground that prevents drug manufacturers from reaping profit windfalls.

Under the exclusivity provisions of the current framework, permissive standards for off-label prescribing often result in taxpayer-funded research. Drug manufacturers may refuse to run pediatric clinical trials on approved drugs that will not generate sufficient profits during the exclusivity-extension period. Such clinical studies would be paid for with tax dollars. The State will have to find a way to generate that revenue, and a way to justify the increased costs to taxpayers—costs many feel should fall squarely on the shoulders of manufacturers, particularly those that have enjoyed billions in profits from government-granted exclusivity periods.<sup>174</sup> This, too, could be improved.

Because many drug manufacturers market several drugs,<sup>175</sup> one way to generate the money needed for clinical trials that manufacturers refuse to run is to retain some of percentage of the drug manufacturer’s profits earned during the six-month exclusivity extension in a trust for future research by that drug company. For example, Schering-Plough reportedly earned \$975 million in profits during its six-month exclusivity period for the prescription allergy drug Claritin; holding as little as one percent of the company’s profits during this period in a trust for future research into the

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<sup>173</sup> H.R. Rep. No. 107-277, *supra* note 118, at 56.

<sup>174</sup> The additional revenue generated by manufacturers as a result of the six-month exclusivity has been as much as 36,000% of the costs of research. *See* Breslow, *supra* note 84, at 168–69.

<sup>175</sup> *See, e.g., Pharmaceutical Products*, ABBOT LABS, [http://www.abbott.com/content/en\\_US/20.20.10:10/product/product\\_category/Product\\_Category\\_Profile\\_0001.htm](http://www.abbott.com/content/en_US/20.20.10:10/product/product_category/Product_Category_Profile_0001.htm) (last visited Nov. 28, 2010) (listing several dozen drugs manufactured by Abbott Laboratories); *Products*, BRISTOL-MYERS SQUIBB, <http://www.bms.com/products/Pages/home.aspx> (last visited Nov. 28, 2010) (listing fourteen products currently marketed by Bristol-Myers Squibb); *Products*, LILLY, <http://www.lilly.com/products/> (listing twenty-three products currently marketed by Eli Lilly and Company).

company's other drugs would ensure that funds would be available for new research, even if the company chooses not to do the research itself.

This is not a perfect solution: six-month exclusivity periods still impose a cost on the consumers of the drug in question, who must pay for the name-brand product while the manufacturer has exclusivity.<sup>176</sup> Given that there are far fewer pediatric off-label drug users than there are taxpayers, it is perhaps more equitable to spread the financial burden across the tax base. Thus, while the trust account solution has the socially desirable result of taking the financial burden off of the taxpayer and shifting it onto the entity that should arguably be funding the research in the first place, the cost to children who are prescribed drugs off-label may be too great.

#### B. DOCTORS' ROLE IN ACQUIRING ADDITIONAL DATA

Some doctors are doing their part to increase the scientific benefits of off-label prescribing by systematically acquiring anecdotal data. Pediatric Research in Office Settings (PROS) is a practice-based research network supported by the U.S. Department of Health and Human Services that was established by the American Academy of Pediatrics (AAP) in 1986.<sup>177</sup> The "mission of PROS is to improve the health of children and enhance primary care practice by conducting national collaborative practice-based research."<sup>178</sup> PROS is organized so that "practitioners and researchers work together to generate research questions, design study materials and protocols, obtain research funding, collect study data, analyze collected data, and publish results."<sup>179</sup> The PROS organization has studied a diverse sample of child health topics and has generated the information underlying the clinical guidelines of the AAP and other organizations.<sup>180</sup>

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<sup>176</sup> See *Recent Developments Which May Impact Consumer Access to, and Demand for, Pharmaceuticals*, FDA.GOV, <http://www.fda.gov/NewsEvents/Testimony/ucml15212.htm> (providing transcript of statement by Janet Woodcock, M.D., director of the Center for Drug Evaluation and Research before the House Committee on Energy and Commerce, on June 13, 2001). Doctor Woodcock noted that the drug reform has required balancing drug development with "expediting the approval of lower-cost generic drugs." *Id.*

<sup>177</sup> See Am. Acad. of Pediatrics, *Pediatric Research in Office Settings*, <http://www.aap.org/pros/abtpros.htm> (last visited March 12, 2009) ("As of March 2005, PROS consists of 1,953 pediatric practitioners from 719 practices in 49 states, Puerto Rico and Canada, teamed with a research staff at AAP headquarters in Elk Grove Village, IL and research consultants from around the country. The network has experienced steady growth since its inception.").

<sup>178</sup> *Id.*

<sup>179</sup> *Id.*

<sup>180</sup> See *id.*

PROS practitioners and researchers could help generate invaluable information by compiling off-label prescription data in a national database. This could make information on the safety and efficacy of drugs available to doctors and patients: information that, up until now, has been available only through clinical studies.

Critics may argue that the information gained through this system would not compare to the information gained through clinical trials because off-label prescriptions are not screened for confounding variables that may be responsible for observed trends. Also, the results would be difficult to standardize if different doctors prescribe different dosages to patients in different groups. The PROS system would, however, produce many more data points<sup>181</sup> than clinical trials. Additionally, the PROS system would alleviate some of the typical concerns associated with child research, such as the financial conflicts of interest associated with recruiting research participants and the dangers of not treating those children in the control group.

#### VII. CONCLUSION: STRIKING THE APPROPRIATE BALANCE

Until recently, children seemed to have been systematically excluded from the protections of the FDCA's "safe and effective" requirements.<sup>182</sup> In amending the 1994 Rule, the FDAMA, BPCA, and PREA have taken steps to address this issue. The incentive structure underlying this framework has achieved considerable success relative to previous efforts; however, the incentive structure is also costly to drug users and taxpayers.

With this in mind, cost effective programs need to be developed to reduce costs and effectively identify drugs that require pediatric testing.<sup>183</sup> One way to do this would be to expand the reach of the PROS practiced-based research network. Pediatricians could collaborate to document otherwise hard-to-find records of off-label use and create a national database of practice-based research that would inform pediatric off-label prescribing practices and assist the FDA in determining which drugs warrant clinical trials. The PROS approach could be implemented concurrently with the existing carrot-and-stick regime of the incentive-structure framework. Regulations should also ensure that manufacturers report *all* post-approval clini-

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<sup>181</sup> The PROS system could generate one data point for each child taking an off-label medication, assuming that enrollment in the program became the norm.

<sup>182</sup> 21 U.S.C. § 355(a)-(d)(3) (2006).

<sup>183</sup> These programs should be developed collaboratively by Congress, physician organizations and drug manufacturers to ensure access to the broadest range of information and funding from both the government as well as those who stand to profit from drug sales.

cal trials, and additional forward-looking measures, such as withholding some of a drug manufacturer's exclusivity-period profits for future research, should also be considered.

President Obama's new healthcare legislation, the Patient Protection and Affordable Care Act ("PPACA"), has attempted to address this issue by initiating "studies regarding pediatric research."<sup>184</sup> The new legislation calls for review and assessment of (1) the importance of testing biological products on children; (2) labeling changes that have resulted from such tests; (3) prioritization of drugs not being tested for pediatric use; and (4) recommendations and incentives for ensuring pediatric testing.<sup>185</sup>

Currently, officials from over twenty states are challenging the PPACA.<sup>186</sup> The most hotly contested provision of the Act is the requirement that Americans obtain insurance.<sup>187</sup> Children deserve to know that the medications prescribed to them are both safe and effective, whether or not the law is ultimately repealed. In the case that it is repealed, the portions of the PPACA calling for pediatric studies of drugs and biological products should be passed as a separate bill.

It may be the gold standard to require pediatric clinical trials for all drugs used by children and adolescents, but manufacturers and the costs of pediatric research have stood in the way of this ideal. Recent improvements, including the PPACA's provisions regarding pediatric research, represent steps in the right direction, but the best scenario would include a collaborative effort by doctors to collect information on drugs not being clinically tested on children. Combining clinical studies and a central doctor-created database of the safety and efficacy of drugs and biological products in children strikes the appropriate balance of ensuring that children are protected from unsafe prescription drugs without hindering the progress of medicine.

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<sup>184</sup> H.R. 3590-702 (2)-(4).

<sup>185</sup> *Id.*

<sup>186</sup> Kevin Sack, *Challenging Health Care Law, Suit Advances*, Oct. 14, 2010, N.Y. TIMES, Oct. 14, 2010, <http://www.nytimes.com/2010/10/15/health/policy/15health.html>.

<sup>187</sup> *Id.*