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THE MYSTERIES OF PREGNANCY: THE ROLE OF LAW IN SOLVING THE PROBLEM OF UNKNOWN BUT KNOWABLE MATERNAL–FETAL MEDICATION RISK

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**THE MYSTERIES OF PREGNANCY: THE ROLE OF LAW IN
SOLVING THE PROBLEM OF UNKNOWN BUT
KNOWABLE MATERNAL–FETAL MEDICATION RISK**

*Kate Greenwood**

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I. INTRODUCTION

The treatment of medical conditions during pregnancy is one of the least developed areas of clinical pharmacology.¹ The resultant uncertainty has a direct impact on patient care, leading to inappropriate

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1. See Catalin S. Buhimschi & Carl P. Weiner, *Medications in Pregnancy and Lactation: Part I. Teratology*, 113 *OBSTETRICS & GYNECOLOGY* 166, 166 (2009). Medication use in breastfeeding women is similarly understudied. *Id.* See also Esther E. Stultz et al., *Extent of Medication Use in Breastfeeding Women*, 2 *BREASTFEEDING MED.* 145, 150 (2007) (finding that over a third of the breastfeeding women surveyed took medications that were rated possibly or probably unsafe or were of unknown safety).

treatment and under treatment. The case of pregnant women infected with the 2009 influenza A (H1N1) virus is instructive. Although seasonal flu can cause severe illness during pregnancy, the “rapid clinical deterioration” seen in some pregnant patients with H1N1 flu appears to be unique.² While pregnant women make up approximately 1% of the United States population, they accounted for 5% of the deaths caused by H1N1 in the United States in 2009.³

As a result of H1N1’s potential to cause severe illness and death in pregnant women, the Centers for Disease Control and Prevention (CDC) recommended that they be among the first inoculated,⁴ and that they take the antiviral medications Tamiflu or Relenza at the first sign of flu symptoms.⁵ Dr. Denise Jamieson of the CDC told the *New York Times* that “the benefit of giving Tamiflu outweighs the risk” for pregnant patients who exhibit classic flu symptoms.⁶ However, neither Tamiflu nor Relenza is well-studied in pregnant women.⁷ The authors of a *New York Times* editorial point out that “[i]t is perfectly possible that the standard adult dose of antivirals will not work in the pregnant body,”⁸ and a group of experts convened by the CDC acknowledges that “[l]ittle is known about the effects of the four currently available anti-influenza medications on the fetus.”⁹

The CDC has determined that in the early months of the pandemic there was no delay in diagnosing pregnant women with the new flu

2. Janice K. Louie et al., *Severe 2009 H1N1 Influenza in Pregnant and Postpartum Women in California*, 362 *NEW ENG. J. MED.* 27, 33 (2010).

3. Alicia M. Siston et al., *Pandemic 2009 Influenza A(H1N1) Virus Illness Among Pregnant Women in the United States*, 303 *JAMA* 1517, 1522–23 (2010).

4. *Id.* at 1523.

5. Donald G. McNeil Jr., *Drugs Urged for Swine Flu in Pregnancy*, *N.Y. TIMES*, May 13, 2009, at A10.

6. *Id.*

7. See Toshihiro Tanaka et al., *Safety of Neuraminidase Inhibitors Against Novel Influenza A(H1N1) in Pregnant and Breastfeeding Women*, 181 *CAN. MED. ASS’N J.* 55, 56–57 (2009) (presenting data derived from a Japanese post-marketing study that followed ninety pregnant women who took Tamiflu in their first trimester, from a report by the manufacturer on sixty-one pregnant women exposed to Tamiflu with unknown timing, from three cases of accidental exposure during clinical trials of Relenza, and from “[a] study using an ex vivo human placenta model”); Highlights of Prescribing Information for Relenza, http://us.gsk.com/products/assets/us_relenza.pdf (last visited Aug. 10, 2010); Highlights of Prescribing Information for Tamiflu, <http://www. Rocheusa.com/products/tamiflu/pi.pdf> (last visited Aug. 10, 2010).

8. Ruth Faden et al., *A Custom Drug*, *N.Y. TIMES*, May 10, 2009, at WK10. See also Sonja A. Rasmussen et al., *Pandemic Influenza and Pregnant Women: Summary of a Meeting of Experts*, 99 *AM. J. PUB. HEALTH* S248, S250 (2009) (“No data are available to address whether dosage adjustment [of anti-influenza medications] is needed; thus, no dosage alterations for pregnant women are recommended at this time.”).

9. Rasmussen et al., *supra* note 8, at S249.

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strain.¹⁰ In many cases, however, there was a delay in beginning treatment with antiviral medication,¹¹ possibly because health care providers, pregnant women, or both were reluctant to begin treatment due to the lack of information about the effectiveness and safety of flu medications during pregnancy.¹² This is unfortunate. A nationwide study of pregnant women with H1N1 flu showed that women who did not begin antiviral treatment until more than four days after symptom onset were fifty-four times more likely to die than women who were treated within two days of symptom onset.¹³

The information gap is not unique to antivirals. We lack data on the efficacy, safety, or both of most drugs when used by pregnant women.¹⁴ This is a significant problem because an estimated two-thirds of the women who give birth in the United States each year are prescribed a drug other than a vitamin or mineral while they are pregnant.¹⁵

Physiological changes caused by pregnancy, including a 30% to 40% increase in blood flowing through the kidneys, “increases in blood volume, decreases in gastric-emptying time, changes in the concentrations of sex hormones, alterations in liver enzymes, [and] the presence (to say the least) of a fetal-placental unit,” can affect the absorption, distribution, and elimination of drugs rendering them more or less efficacious.¹⁶ For example, while the American College of Obstetricians and Gynecologists recommends that pregnant women be treated with amoxicillin in the event of anthrax exposure, recent

10. Denise J. Jamieson et al., *H1N1 2009 Influenza Virus Infection During Pregnancy in the USA*, 374 *THE LANCET* 451, 456 (2009).

11. *Id.*; Louie et al., *supra* note 2, at 33. See also Allison L. Naleway et al., *Delivering Influenza Vaccine to Pregnant Women*, 28 *EPIDEMIOLOGIC REV.* 47, 49 (2006) (reporting that pregnant women had the lowest flu vaccine coverage level of all adult groups recommended to receive the vaccine, perhaps due to their expressed concerns about vaccine safety). A recent study found a similar problem with regard to antihypertensive drugs noting “site-specific differences” in the rate of use of such drugs to treat pregnant women with high blood pressure. Susan E. Andrade et al., *Outpatient Use of Cardiovascular Drugs During Pregnancy*, 17 *PHARMACOEPIDEMIOLOGY & DRUG SAFETY* 240, 246 (2008). The researchers who conducted the study suggested that health care providers’ uncertainty about how to manage hypertension during pregnancy given limited knowledge about the risk-to-benefit profile of the various medications could explain the treatment differences. *Id.*

12. Jamieson et al., *supra* note 10, at 456.

13. Siston et al., *supra* note 3, at 1521.

14. Anne Drapkin Lyerly et al., *The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research*, 1 *INT’L J. OF FEMINIST APPROACHES TO BIOETHICS* 6, 7 (2008); Allen A. Mitchell, *Systematic Identification of Drugs that Cause Birth Defects – A New Opportunity*, 349 *NEW ENG. J. MED.* 2556, 2556–57 (2003) (explaining that “the vast majority of medications currently in use have not been studied in a way that would reveal moderate teratogenic risks,” which the author defines as a risk two to ten times greater than the base-line risk for a specific birth defect).

15. Susan E. Andrade et al., *Prescription Drug Use in Pregnancy*, 191 *AM. J. OBSTETRICS & GYNECOLOGY* 398, 400 (2004).

16. Lyerly et al., *supra* note 14, at 8.

pharmacokinetic research indicates that changes to kidney function during pregnancy may make it impossible to give a pregnant woman a high enough dose of the antibiotic for it to be effective against anthrax.¹⁷ Similarly, blood concentrations of antimalarial and diabetes drugs have been shown to be reduced in pregnant women such that higher doses than are currently recommended are needed.¹⁸

Pregnancy also creates special safety concerns. Because most drugs pass from the mother's blood through the placenta to the fetus, a pregnant woman deciding to take a drug needs to know its potential to cause teratogenic harm.¹⁹ Teratogens are "agents that act to irreversibly alter growth, structure, or function of the developing embryo or fetus."²⁰ They include certain chemicals (e.g., alcohol, mercury), environmental conditions (e.g., heat, radiation), and viruses (e.g., cytomegalovirus, rubella) as well as some therapeutic drugs.²¹ Complicating matters, a drug's teratogenic and other ill effects can vary by gestational age. During the period of organogenesis, which occurs between three and eight weeks after fertilization, each organ system has a period of peak vulnerability.²² For example, spina bifida and related defects arise during the process of neurulation, which occurs between seventeen and thirty days after fertilization.²³ The heart is most vulnerable between six and a half and eight weeks of gestation.²⁴ Nonsteroidal anti-inflammatory drugs like aspirin and ibuprofen can cause, among other problems, the abdominal wall defect gastroschisis when taken in early pregnancy; in late pregnancy, they can cause premature closure of the ductus arteriosus, a heart defect.²⁵ A recently published study suggested that in the case of serotonin reuptake inhibitors, a widely prescribed class of antidepressant medication, the timing of in utero exposure may

17. American College of Obstetricians and Gynecologists, *Management of Asymptomatic Pregnant or Lactating Women Exposed to Anthrax*, 77 INT'L J. GYNECOLOGY & OBSTETRICS 293, 294–95 (2002); Anne Drapkin Lyerly et al., *The National Children's Study: A Golden Opportunity to Advance the Health of Pregnant Women*, 99 AM. J. PUB. HEALTH 1742, 1742 (2009) (citing M.A. Andrew et al., *Amoxicillin Pharmacokinetics in Pregnant Women: Modeling and Simulations of Dosage Strategies*, 81 CLINICAL PHARMACOLOGY & THERAPEUTICS 547, 547–56 (2007)).

18. Lyerly et al., *supra* note 17, at 1742 (citing M.F. Herbert et al., *Are We Optimizing Gestational Diabetes Treatment with Glyburide? The Pharmacologic Basis for Better Clinical Practice*, 85 CLINICAL PHARMACOLOGY & THERAPEUTICS 607, 607–14 (2009)); Nicholas J. White et al., *New Medicines for Tropical Diseases in Pregnancy: Catch-22*, 5 PLOS MED. 843, 843 (2008).

19. Catalin S. Buhimschi & Carl P. Weiner, *Medications in Pregnancy and Lactation: Part I. Teratology*, 113 OBSTETRICS & GYNECOLOGY 166, 167 (2009).

20. *Id.* at 167.

21. *Id.*

22. *Id.* at 168.

23. *Id.*

24. *Id.*

25. *Id.*

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be less important than the duration.²⁶

Our profound ignorance about what drug to use and when to use it has a number of negative repercussions. On the one hand, of necessity health care providers prescribe medications to pregnant women “off-label,” that is, without FDA-approved dosing or other guidance; for some of these drugs, the risk of harm outweighs any potential for therapeutic gain.²⁷ On the other hand, the lack of data leads to “lost therapeutic opportunities.”²⁸ It causes some health care providers to recommend that pregnant women forego needed treatment that would, on balance, reduce the risk of harm to them and their fetuses.²⁹ It causes other health care providers to choose older medications they believe to be safe over newer drugs that may have important therapeutic or safety advantages for pregnant women and their fetuses.³⁰ The information gap also results in medications being prescribed in doses too low to be effective or higher than necessary to achieve a therapeutic benefit while minimizing the risk of fetal harm.³¹ Finally, when a fetus is inadvertently exposed to medication in early pregnancy, terminating the pregnancy may be considered.³² An unknown risk of birth defects could cause some women to terminate wanted pregnancies.³³

While many medical decisions could benefit from better information,³⁴ the lack of data about the treatment of medical conditions

26. Tim F. Oberlander et al., *Effects of Timing and Duration of Gestational Exposure to Serotonin Reuptake Inhibitor Antidepressants: Population-Based Study*, 192 BRIT. J. PSYCHIATRY 338, 341–42 (2008).

27. Lyerly et al., *supra* note 14, at 10–11.

28. Barbara A. Noah, *Just a Spoonful of Sugar: Drug Safety for Pediatric Populations*, 37 J.L. MED. & ETHICS 280, 281 (2009) (discussing the lack of information about the safety and efficacy of drugs when used in pediatric populations).

29. Lyerly et al., *supra* note 14, at 11–13.

30. See, e.g., Michelle Meadows, *Pregnancy and the Drug Dilemma*, 35 FDA CONSUMER 16, 18 (2001) (quoting Catherine Stika, a physician and assistant professor of obstetrics and gynecology at Northwestern University School of Medicine, as follows: “We’ll prescribe an older hypertension drug because its long history hasn’t turned up serious safety concerns. . . . There may be other drugs that are more effective and better tolerated, but we don’t use them because we don’t know about their safety.”).

31. Content and Format of Labeling for Human Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,844 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

32. *Id.* at 30,834.

33. *Id.* See also Gideon Koren et al., *Drugs in Pregnancy*, 338 NEW. ENG. J. MED. 1128, 1134 (1998) (“Women often report that their physicians have encouraged them to terminate otherwise wanted pregnancies just to be on the safe side, suggesting that many physicians are unfamiliar with the current literature on the safety of drugs taken during pregnancy.”). Cf. Anne Drapkin Lyerly et al., *Risk and the Pregnant Body*, HASTINGS CENTER REP., Nov.–Dec. 2009, at 34, 36 (discussing a study in which 5% of obstetricians and family physicians surveyed reported that they would recommend abortion to patients who had a radiologic scan in early pregnancy based on their (mistaken) perceptions of teratogenic risk).

34. See Lars Noah, *Medicine’s Epistemology: Mapping the Haphazard Diffusion of Knowledge*

during pregnancy is particularly troubling. The medical decisions that pregnant women and their health care providers make are complicated by the fact that they must account for two interdependent patients instead of the usual one, and the stakes are high. In addition, as Anne Drapkin Lyerly and her co-authors have noted, there is reason to question our ability to reason about risk during pregnancy.³⁵ Women and their health care providers have been shown to overestimate the risk that drugs will cause serious birth defects.³⁶ Lyerly, a practicing obstetrician, writes that “[w]hen treating pregnant women’s nonobstetrical medical needs, it turns out, there is a tendency to notice the risks of intervening without adequately noting the risks of *failing* to intervene.”³⁷ She concludes that in pregnancy “a particularly unfettered version of the precautionary principle” too often replaces evidence-based recommendations.³⁸ The cultural norm of purity in pregnancy and our reluctance to confront potential trade-offs between maternal and fetal interests further hinder our ability to reason about medication risk and pregnancy.³⁹ While Lyerly and her colleagues argue that maternal–fetal interests are more often aligned than not, conflicts can occur.⁴⁰ All of these factors make it especially important that treatment decisions in pregnancy not be made in ignorance.

A frequent shorthand explanation for the dearth of information about the safety and efficacy of drugs when used during pregnancy is that you cannot test drugs on pregnant women because of ethical concerns.⁴¹ Real moral conundrums arise in maternal–fetal medicine and there will always be information that is out of reach because it can only be gleaned from clinical trials that are ethically impermissible.⁴² This alone does

in the Biomedical Community, 44 ARIZ. L. REV. 373, 389 (2002) (“[N]o one denies that many medical treatments remain seriously understudied.”).

35. Lyerly et al., *supra* note 33, at 35.

36. Content and Format of Labeling for Human Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,844 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201) (citing sources).

37. Anne Drapkin Lyerly et al., *Risk and the Pregnant Body*, HASTINGS CENTER REP., Nov.–Dec. 2009, at 35.

38. *Id.* at 39.

39. *Id.*

40. *Id.* at 40.

41. See, e.g., Liz Szabo, *A ‘Drug Drought’ for Pregnant Women*, USA TODAY, June 3, 2008, available at http://www.usatoday.com/news/health/2008-06-03-pregnant-drugs_N.htm (reporting that Alan Goldhammer, deputy vice president of regulatory affairs for PhRMA, the trade organization which represents many pharmaceutical and biotechnology companies, said that although drug makers would like to develop drugs for pregnancy complications, they have to consider the potential harmful effects that experimental drugs could have on a fetus).

42. Lyerly et al., *supra* note 17, at 2. See also The Am. Coll. of Obstetricians & Gynecologists Comm. on Ethics, *Ethical Considerations in Research Involving Pregnant Women*, 65 INT’L J.

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not explain the information gap. First, not all clinical trials in pregnant women are unethical.⁴³ Second, data derived from other types of investigations that are ethically unproblematic, for example, pharmacokinetic studies in pregnant women taking a medication as part of their prescribed treatment regimen, are also lacking, as are epidemiological data.

Existing statutory and regulatory levers do elicit private-sector drug research, the research required to monetize a patent, for example, along with the research necessary to secure permission to sell a prescription drug, to market an approved drug for a heretofore unapproved use, and to make certain promotional claims about a drug. However, they do not generate adequate research into the safety and efficacy of drugs when used during pregnancy. Because these levers hinge on the existence of profitable potential markets for the drugs studied, they ill-serve the relatively small and transient pregnant patient population. Federal regulations and guidance that affirmatively limit the testing of drugs in pregnant women for ethical and other reasons further slow the pace of maternal–fetal medication research.

The common law fails to fill the information gap. A company has an incentive to study a drug to the extent that detecting safety issues early reduces the number of injuries caused by that drug and, therefore, the company's exposure to damage awards. Companies must also consider the risk of liability for failing to warn of risks for which they unreasonably failed to test. These incentives are weighed against companies' exposure to liability for harms incurred by research participants. Moreover, when research reveals that a drug previously believed to be safe in fact causes harm, lawsuits inevitably follow. This is true even in cases where the company acted responsibly. Finally, many observers believe that maternal–fetal medication research is especially susceptible to a "liability barrier," because of the high

GYNECOLOGY & OBSTETRICS 93 (1999).

43. See Laurence B. McCullough et al., *A Comprehensive Ethical Framework for Responsibly Designing and Conducting Pharmacologic Research that Involves Pregnant Women*, 193 AM. J. OBSTETRICS & GYNECOLOGY 901 (2005). The medical literature provides multiple examples of placebo-controlled studies in pregnant women, suggesting that there are circumstances in which the risk-benefit ratio of such research is favorable. See, e.g., Mark B. Landon et al., *A Multicenter, Randomized Trial of Treatment for Mild Gestational Diabetes*, 361 NEW ENG. J. MED. 1339, 1339 (2009); Dwight J. Rouse et al., *A Randomized, Controlled Trial of Magnesium Sulfate for the Prevention of Cerebral Palsy*, 359 NEW ENG. J. MED. 895, 895 (2008); Debra A. Guinn et al., *Terbutaline Pump Maintenance Therapy for Prevention of Preterm Delivery: A Double-Blind Trial*, 179 AM. J. OBSTETRICS & GYNECOLOGY 874 (1998); Debra A. Guinn et al., *Management Options in Women with Preterm Uterine Contractions: A Randomized Clinical Trial*, 177 AM. J. OBSTETRICS & GYNECOLOGY 814 (1997); see also Steve Sternberg, *Pregnant Women Taking Part in New H1N1 Vaccination Trials*, USA TODAY, Sept. 10, 2009, available at http://www.usatoday.com/news/health/2009-09-10-pregnant-swine-flu-vaccine_N.htm.

background rate of birth defects, because of the potential for large damage awards, and because of the “long tail” of associated litigation.

This Article proceeds as follows. Part II assesses our current state of ignorance about the safety and efficacy of drugs when used during pregnancy. Part III sets forth the existing statutory and regulatory levers to elicit private-sector drug research and explains why neither they nor the tort system generate sufficient maternal–fetal medication research. Part IV evaluates two oft-mentioned policy responses to an underproduction of medical research, (1) eliminating (or muting the effect of) the liability barrier facing pharmaceutical companies and (2) offering an extended period of exclusivity to incentivize private-sector research, and concludes that both are, on balance, undesirable approaches to increasing our understanding of maternal–fetal medication risk.

Instead, Part IV recommends that federal and state governments increase their support for maternal–fetal medication research, including through innovative public-private partnerships like the FDA’s recently announced Medication Exposure in Pregnancy Risk Evaluation Program⁴⁴ and its Sentinel System.⁴⁵ Industry can and should do more as well. Congress should require pharmaceutical companies to conduct an assessment of maternal–fetal medication risk as part of the new drug approval process, and it should empower the FDA to require that companies study their already-approved drugs in pregnant women, steps that have already been taken in the pediatric arena. In the meantime, the FDA should make full use of its existing authority to require post-marketing surveillance, including the establishment of pregnancy registries, as a condition of drug approval and to require manufacturers to conduct post-marketing studies and clinical trials when questions arise about the safety of their drugs in pregnant women.

II. THE MATERNAL–FETAL MEDICATION RISK INFORMATION GAP

The dearth of information about the treatment of medical conditions during pregnancy is a significant problem. In the United States, there are over sixty million women of childbearing age, defined for statistical purposes as between the ages of fifteen and forty-four.⁴⁶ More than nine

44. Press Release, U.S. Dept. of Health & Human Servs., Food & Drug Admin., Health Organizations to Study Safety of Medications Taken During Pregnancy (Dec. 30, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm195934.htm>.

45. U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., FDA’S SENTINEL INITIATIVE, <http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm> (last visited Aug. 12, 2010).

46. Content and Format of Labeling for Human Prescription Drugs and Biological Products;

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million of them have chronic conditions that require ongoing prescription drug treatment during pregnancy to protect their health and the health of their fetuses.⁴⁷ Millions more develop a new medical condition or experience the exacerbation of an old one while they are pregnant.⁴⁸

Asthma, for example, is prevalent in pregnancy, afflicting approximately 8% of pregnant women.⁴⁹ There is a strong association between poor asthma control during pregnancy and health problems for the baby, including intrauterine growth restriction, preeclampsia, preterm birth, low birth weight, birth defects, and perinatal death.⁵⁰ Poor asthma control during pregnancy also has a direct effect on the pregnant woman, increasing serious risks to her health and life.⁵¹ Despite these findings, only two randomized controlled trials involving pregnant women with asthma have been conducted, and, as a result, the “mechanisms linking poorly controlled asthma to adverse perinatal outcomes remain unclear.”⁵²

Diabetes diagnosed prior to and during pregnancy is also common—occurring in just over 4% of pregnancies that end in birth.⁵³ Diabetes is becoming increasingly prevalent during pregnancy; since 2003, it has increased at a rate of 6–7% per year.⁵⁴ Pregnancy-induced hypertension is common too, occurring in just under 4% of pregnancies, while chronic hypertension complicates another 1% of pregnancies.⁵⁵ Like the diabetes rate, the hypertension rate during pregnancy has been increasing every year in recent years.⁵⁶ One possible explanation is the rise in the pregnancy and birth rate among women forty years of age and older, as the proportion of women receiving an antihypertensive

Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,844 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

47. *Id.*

48. *Id.* at 30,841 (noting that depression and migraine headaches can be exacerbated by pregnancy).

49. Michael Schatz & Mitchell P. Dombrowski, *Asthma in Pregnancy*, 360 NEW ENG. J. MED. 1862, 1862 (2009).

50. *Id.*

51. *Id.*

52. *Id.* at 1864, 1866. Conducting controlled trials “to determine the effects of asthma control, as compared with lack of control, on perinatal outcomes” is not possible due to ethical concerns. *Id.* at 1866.

53. Joyce A. Martin et al., Ctrs. for Disease Control & Prevention, Nat’l Vital Statistics Reports, *Births: Final Data for 2006*, Jan. 7, 2009, at 13, available at http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57_07.pdf.

54. *Id.*

55. *Id.* at 14.

56. *Id.*

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medication increases with age.⁵⁷ Other diseases occurring during pregnancy include autoimmune diseases, cancer, epilepsy, and psychiatric illness, which complicates an estimated 500,000 pregnancies.⁵⁸

More than four million women give birth in the United States each year⁵⁹ and many of them take medication during their pregnancies. A 2004 study conducted by Susan Andrade and colleagues of the electronic medical records of over 150,000 women located throughout the United States who received prenatal care between 1996 and 2000 revealed that 64% were dispensed at least one medication other than a vitamin or mineral supplement.⁶⁰ A 2003 study in which close to six hundred rural obstetric patients in West Virginia were interviewed on multiple occasions about medication use found that, excluding prenatal vitamins and minerals, about 60% took a prescription medication during their pregnancy.⁶¹

There is also unintended drug use during pregnancy. Every year, an estimated 10% of women between the ages of fifteen and forty-four become pregnant;⁶² nearly half of these pregnancies are unplanned.⁶³ A 2002 survey found that 82% of women eighteen to forty-four years old had used some type of medication during the preceding week, 46% used a prescription drug, and 3% used five or more prescription drugs.⁶⁴ As

57. Andrade et al., *supra* note 11, at 243.

58. Lyerly et al., *supra* note 14, at 6 (reporting that autoimmune diseases and cancer “commonly occur with pregnancy and often require treatment”); Pamela Paul, *With Child, With Cancer*, N.Y. TIMES, Aug. 31, 2008, at MM34 (reporting that the estimated rate of pregnancy-associated cancer is 1 in 1000); Torbjörn Tomson, *Which Drug for the Pregnant Woman with Epilepsy?*, 360 NEW. ENG. J. MED. 1667, 1667 (2009) (noting that approximately 25,000 children are born to mothers with epilepsy each year and that most women with epilepsy must continue taking medication to treat it during pregnancy); AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS, ACOG PRACTICE BULLETIN NO. 92, USE OF PSYCHIATRIC MEDICATIONS DURING PREGNANCY AND LACTATION (2008).

59. Stephanie J. Ventura et al., Ctrs. for Disease Control & Prevention, Nat'l Vital Statistics Reports, *Estimated Pregnancy Rates by Outcome for the United States, 1990–2004*, Apr. 14, 2008, at 1, available at http://www.cdc.gov/nchs/data/nvsr/nvsr56/nvsr56_15.pdf.

60. Susan E. Andrade et al., *Prescription Drug Use in Pregnancy*, 191 AM. J. OBSTETRICS & GYNECOLOGY 398, 400 (2004).

61. Douglas D. Glover et al., *Prescription, Over-the-Counter, and Herbal Medicine Use in a Rural, Obstetric Population*, 188 AM. J. OBSTETRICS & GYNECOLOGY 1039, 1041 (2003).

62. Ventura et al., *supra* note 59, at 12. There are approximately six million pregnancies per year in the United States. Press Release, U.S. Dept. of Health & Human Servs., Food & Drug Admin., FDA Proposes New Rule to Provide Updated Information on the Use of Prescription Drugs and Biological Products during Pregnancy and Breast-feeding (May 28, 2008), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116902.htm>.

63. CTRS. FOR DISEASE CONTROL & PREVENTION, PREGNANCY RISK ASSESSMENT MONITORING SYSTEM (PRAMS): PRAMS AND UNINTENDED PREGNANCY, <http://www.cdc.gov/prams/PDFs/PRAMSUnintendPreg.pdf> (last visited Feb. 27, 2010).

64. David W. Kaufman, et al., *Recent Patterns of Medication Use in the Ambulatory Adult*

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these statistics suggest, many women unwittingly expose their fetuses to one or more medications before realizing that they are pregnant.⁶⁵ Such exposure typically occurs in the critical window between three and eight weeks after conception when the fetus' organs develop.⁶⁶

The FDA approves most drugs without any evidence of safety or efficacy when used during pregnancy.⁶⁷ The situation does not improve post-approval, as evidenced by the fact that 60% of prescription drugs are classified by the FDA as category C,⁶⁸ indicating either that (1) a drug has not been studied in either pregnant animals or pregnant women or that (2) adequate and well-controlled studies in pregnant women have not been conducted, animal studies show the drug poses a risk to the fetus, but the drug's benefits may outweigh the potential risk.⁶⁹ Less

Population of the United States: The Slone Survey, 287 JAMA 337, 339 (2002).

65. Content and Format of Labeling for Human Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,841 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201). While inadvertent exposure most commonly occurs in early pregnancy, it can occur at any stage. *Id.*

66. *Id.*

67. *Id.*; Caroline T. Lagoy et al., *Medication Use During Pregnancy and Lactation: An Urgent Call for Public Health Action*, 14 J. WOMEN'S HEALTH 104, 105 (2005).

68. Content and Format of Labeling for Human Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,834 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

69. Under the current regulations, prescription drug labels must include a "Pregnancy" section with information about the drug's potential to cause birth defects as well as any other reproductive effects. *Id.* at 30,832. Each product is assigned a letter—A, B, C, D, or X—based on its potential to cause reproductive and developmental adverse effects. *Id.* at 30,832–33. For categories C, D, and X, a drug's potential to cause harm is weighed against its potential benefit, meaning that the only difference between a drug in category X and a drug in category D could be that there is a safer alternative to the drug in category X. *See id.* at 30,833. The five categories are defined as follows. A drug is category A if adequate and well-controlled studies have been conducted in pregnant women and shown no "risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)." 21 C.F.R. § 201.57(c)(9)(i)(A)(1) (2010). A drug is category B if animal studies have been conducted and shown no risk but there are no adequate and well-controlled studies in pregnant women, or if animal studies have shown a risk but adequate and well-controlled studies in pregnant women have been conducted and did not show a risk. *Id.* § 201.57(c)(9)(i)(A)(2). Category C covers drugs the risks of which have not been studied in pregnant animals or pregnant women; it also covers drugs that animal studies have shown pose a risk to the fetus and that have not been studied in pregnant women, if the drug's benefits may outweigh its potential risks. *Id.* § 201.57(c)(9)(i)(A)(3). Category D is used:

If there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks (for example, if the drug is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective).

Id. § 201.57(c)(9)(i)(A)(4). Finally, category X is for drugs for which the risk of use in pregnant woman clearly outweighs any possible benefit. *Id.* § 201.57(c)(9)(i)(A)(5). In 2008, the FDA issued proposed amendments to the pregnancy labeling regulations which would abolish the category system and replace it with a narrative format that the agency believes would better capture the "complexity of medical decisionmaking about drug use during pregnancy." Content and Format of Labeling for Human

than 1% of drugs fall into category A, which is reserved for drugs the safety of which has been demonstrated by adequate and well-controlled studies in pregnant women.⁷⁰ In 2002, researchers found that the risks posed to the fetus by more than 90% of the prescription drugs approved in the United States between 1980 and 2000 remained unknown.⁷¹ The same researchers found that it took an average of six years after FDA approval for drugs posing a substantial teratogenic risk to be recognized as dangerous, and an average of nine years after FDA approval for drugs posing no more than a minimal teratogenic risk to be recognized as safe.⁷²

Many of the drugs used by pregnant women have not been shown to be safe or have been associated with a risk of fetal harm. The 2004 Andrade research revealed that 37.8% of the women studied were prescribed a drug from category C while pregnant, 4.8% from category D, indicating that there is evidence the drug could cause fetal harm but the benefits may outweigh the risk, and 4.6% from category X, indicating that the risk of use during pregnancy clearly outweighs any possible benefit.⁷³ Andrade and colleagues also analyzed a sub-group of 129,616 deliveries and found that, after excluding contraceptives and other hormones, which may be classified as category D or X but which the evidence suggests are unlikely to have teratogenic effects,⁷⁴ and drugs used to treat infertility, which may similarly be classified as D or X but which are continued through early pregnancy under some protocols,⁷⁵ 3% of pregnant women received at least one dispensing of a category D or X drug.⁷⁶ Another study of the electronic medical records

Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,838 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201). On April 26, 2010, the Department of Health & Human Services announced that the FDA would release the final regulation by March 2011. Semiannual Regulatory Agenda, 75 Fed. Reg. 21,782, 21,795 (Apr. 26, 2010).

70. Buhimschi & Weiner, *supra* note 1, at 170.

71. W.Y. Lo & J.M. Friedman, *Teratogenicity of Recently Introduced Medications in Human Pregnancy*, 100 OBSTETRICS & GYNECOLOGY 465, 468 (2002).

72. *Id.* at 472.

73. Andrade et al., *supra* note 15, at 400. In addition, 2.1% received a drug unrated by the FDA. *Id.*

74. Susan E. Andrade et al., *Use of Prescription Medications with a Potential for Fetal Harm Among Pregnant Women*, 15 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 546, 551 (2006) (noting that the “preponderance of data now suggests unlikely teratogenic potential” for oral contraceptives). Oral contraceptives are used during the early part of about 1% of pregnancies. Buhimschi & Weiner, *supra* note 1, at 181 (noting that this estimate may be low because the authors did not evaluate drug use in pregnancies that did not go to term whether due to abortion or miscarriage).

75. Erika Hyde Riley et al., *Correlates of Prescription Drug Use During Pregnancy*, 14 J. WOMEN’S HEALTH 401, 402–03 (2005).

76. Andrade et al., *supra* note 15, at 400.

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of over 100,000 women who received prenatal care during the same time period found that 3.6% were prescribed a drug in category D while pregnant and 2.4% a drug in category X.⁷⁷ A smaller study of 1,626 women who were pregnant between 2001 and 2003 found that 3.9% were prescribed a category D or X drug other than progestins, which are used to treat infertility.⁷⁸ Finally, a study of data from the National Ambulatory Medical Care and National Hospital Ambulatory Medical Care Survey found that 6.4% of office visits made by pregnant women in 1999 and 2000 were associated with the prescription, provision, or continuation of a category D or X drug.⁷⁹

Studies from other countries have also shown high levels of use of drugs with established or potential fetal risk, including a study of nearly 82,000 British women who were pregnant between 1991 and 1999, which found that in the first trimester 34.5% were prescribed a category C drug, 1.6% a category D drug, and 1.0% a category X drug.⁸⁰ A study of over 18,000 Canadian woman who gave birth between 1997 and 2000 showed that one in five pregnant women used a drug with established or unknown fetal risk that the FDA has classified as category C, category D, or category X.⁸¹ Another widely cited study tracked all of the original prescriptions issued throughout the pregnancies of 1,000 women in 1996 in southwest France and found that 59% were prescribed a category D medication and that 1.6% were prescribed one or more category X medications.⁸² Nearly 80% were exposed to drugs that were uncategorized by the FDA and for which there is no evidence of safety in pregnancy.⁸³

The evidence that large numbers of pregnant women are prescribed

77. Andrade et al., *supra* note 74, at 549. This study also included an evaluation by an expert in teratogenicity who found that 1.1% of pregnant women received a teratogenic drug after their first prenatal care visit and that 0.3% received four or more dispensings of a known teratogen. *Id.*

78. Riley et al., *supra* note 75, at 404.

79. Euni Lee et al., *National Patterns of Medication Use During Pregnancy*, 15 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 537, 540 (2006).

80. Janet R. Hardy et al., *Safety of Medications Prescribed Before and During Early Pregnancy in a Cohort of 81,975 Mothers from the UK General Practice Research Database*, 15 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 555, 562 (2006).

81. S.W. Wen et al., *Patterns of Pregnancy Exposure to Prescription FDA C, D and X Drugs in a Canadian Population*, 28 J. PERINATOLOGY 324 (2008). Among this study's disturbing findings is the fact that trimethoprim/sulfamethoxazole was the antibiotic most frequently prescribed to pregnant women. *Id.* at 327. Trimethoprim/sulfamethoxazole is a folic acid antagonist that can cause birth defects and other problems in newborns. *Id.* There are alternative antibiotics which are equally effective. *Id.* This suggests that generating safety and efficacy information is only one piece of a larger puzzle. In addition to information gaps, there are dissemination gaps.

82. I. Lacroix et al., *Prescription of Drugs During Pregnancy in France*, 356 THE LANCET 1735, 1735–36 (2000).

83. *Id.* at 1736.

drugs that are known to be harmful could be evidence of calculated risks taken by women and their health care providers,⁸⁴ or of provider error or ignorance.⁸⁵ The widespread use of prescription drugs of unknown risk, on the other hand, is evidence of an information gap.

III. EXISTING LEGAL AND REGULATORY LEVERS TO ELICIT PRIVATE-SECTOR DRUG RESEARCH

As Rebecca Eisenberg has observed, the social value of better information about the efficacy and safety of prescription drugs greatly exceeds the value of that information to the private firms which manufacture the drugs.⁸⁶ When clinical trials and other information-generating activities reveal that a drug is more effective or safer than previously believed, only some of the value generated can be recouped by the firm. When the news is bad, the firm recoups nothing. Patients benefit, as can health care providers, payors (including the government), and firms that sell substitute drugs, but the company that sponsored the research does not benefit and is in fact harmed.⁸⁷ A company that studies one of its already-approved drugs risks “generating results that could destroy the value of the product rather than enhance it.”⁸⁸ Benjamin Roin has suggested that there is also a disconnect on the cost side of the equation, with sponsoring companies internalizing clinical trial costs in excess of the trials’ costs to society.⁸⁹ This could occur when a sponsor bears the cost of study participants’ medical care.⁹⁰

For these reasons, motivating firms to study their drugs is “a major challenge for the legal system.”⁹¹ Below I discuss four legal regimes that affect firms’ incentives to invest in information development: (1) patents; (2) the FDA approval process, including FDA-administered

84. Riley et al., *supra* note 75, at 408 (“Although the prenatal use of many of the category D and X drugs identified in our analysis may place women or their unborn children at unnecessary risk, some of these drugs may have been prescribed after careful consideration that benefits outweigh the risks.”).

85. *See id.* at 401 (noting that there are safer alternatives for many of the category D and X medications that pregnant women are prescribed); Noah, *supra* note 34, at 377 (“[W]e already have evidence-based medicines, but we most certainly do not yet enjoy fully evidence-based medical practice.”).

86. Rebecca S. Eisenberg, *The Problem of New Uses*, 5 YALE J. HEALTH POL’Y L. & ETHICS 717, 718 (2005).

87. *Id.*

88. *Id.* This risk may be lessened in the maternal–fetal context, because a finding that a drug is unsafe for use during pregnancy could leave its broader market unaffected.

89. Benjamin N. Roin, *Unpatentable Drugs and the Standards of Patentability*, 87 TEX. L. REV. 503, 563 (2009).

90. *Id.*

91. Eisenberg, *supra* note 86, at 719–20.

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periods of exclusivity that can supplement the patent regime's market exclusivity period, the pre-approval reproductive toxicity testing the agency requires, and the ethical limits the agency places on testing drugs in pregnant women; (3) the FDA's regulation of pharmaceutical marketing and the incentive it creates for companies to conduct research into "off-label" drug uses; and (4) the tort system.⁹²

A. Research Required to Monetize a Drug Patent

As Eisenberg observes, "[d]rugs are information-rich chemicals that in many respects are more akin to other information products (such as databases) than they are to other chemicals (such as industrial solvents)."⁹³ In the absence of information about their safety and efficacy in humans, drugs would not be drugs, and there would be no market for them. Firms must invest in information development to create a market for their drugs, but would not do so if competitor firms could immediately free ride on their investment.⁹⁴ By excluding would-be free riders from the market for twenty years, the patent regime sets the stage for pharmaceutical firms to profit from the costs of establishing a drug's safety and efficacy for a particular use.⁹⁵

The protection the patent regime provides for firms' investment in research into new uses for existing drugs, including their use in specific subpopulations, is much weaker. While a firm can secure a patent for a new use, this would not stop competitors from manufacturing and selling the drug for the old use.⁹⁶ In theory, the innovator firm could sue

92. Firms are, of course, also subject to a host of other incentives unrelated to the legal regimes discussed. To give just one example, insurance reimbursement may be conditioned on scientifically sound safety and efficacy evidence. See Stephen Siciliano, *Randomized Clinical Trial Said Needed to Gain Payment for Novel Therapeutic*, 4 LIFE SCI. L. & INDUS. REP. 236, 236 (2010). Cf. AETNA, CLINICAL POLICY BULLETIN: TERBUTALINE PUMP FOR PRETERM LABOR, http://www.aetna.com/cpb/medical/data/400_499/0468.html (last visited Apr. 30, 2010) (summarizing the existing evidence on the use of the asthma medication terbutaline off-label for preventing or treating preterm labor and determining that the use was "experimental and investigational," that is, unlikely to be reimbursed).

93. Eisenberg, *supra* note 86, at 717.

94. *Id.* at 721; Kevin Outterson, *Pharmaceutical Innovation: Law & the Public's Health*, 37 J.L. MED. & ETHICS 173, 173 (2009) ("While empirical research suggests that patents are an ineffective incentive for innovation generally, patents retain their paradigmatic function in the pharmaceutical and chemistry industries.").

95. Eisenberg, *supra* note 86, at 721.

96. *Id.* at 724. *But see* *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 601 F.3d 1359, 1365 (Fed. Cir. 2010) ("This court perceives that the Hatch-Waxman Act will thus ensure that a generic drug for non-patented purposes will not be used for patented purposes via a simple section viii certification. Instead, the generic manufacturer will need to alleviate the risk of infringement or induced infringement in a proceeding that fully tests for infringement and its implications, including potential health and safety risks.").

any generic manufacturer who promotes the drug for the new, infringing use, as well as the doctors, pharmacists, and patients who prescribe, dispense, and take the drug. This avenue is undesirable for a number of reasons, including that “few industries prosper by suing customers.”⁹⁷

Research into the safety and efficacy of a new drug when used during pregnancy is not required to create a market for the drug and thereby monetize the asset. For example, a drug that treats diabetes or hypertension need only be shown effective at stabilizing blood sugar or blood pressure for there to be a market for it. Its efficacy and safety in pregnancy can remain unknown.

The failure of the patent regime to incentivize the development of drug treatments for pregnancy-specific conditions such as miscarriage, intrauterine growth restriction, preeclampsia, placental abruption, and preterm birth is a related but distinct problem, one that this Article does not address. Briefly, despite the devastation these conditions cause, obstetric drug development proceeds at a glacial pace.⁹⁸ The FDA has not approved a new class of drugs to treat pregnancy complications for two decades, and as there are no first-generation drugs in clinical trials now, none is likely to be approved for at least another decade.⁹⁹

B. Research Required for Permission to Sell a Prescription Drug

The patent regime’s incentive to conduct research and development is supplemented by the federal Food, Drug, and Cosmetic Act (FD&C Act) requirement that prescription drugs be approved by the FDA before they

97. Eisenberg, *supra* note 86, at 724.

98. Obstetrics has been called the “the least scientific specialty in medicine,” in part because the mainstays of its drug formulary “hark back to an earlier era.” Nicholas M. Fisk & Rifat Atun, *Market Failure and the Poverty of New Drugs in Maternal Health*, 5 PLOS MED. 22, 22 (2008). See also ATUL GAWANDE, BETTER: A SURGEON’S NOTES ON PERFORMANCE 188 (2007). A recent study which compared drug development in maternal health with the drug pipelines for cardiovascular disease, a mainstream but not leading specialty area, and amyotrophic lateral sclerosis, an orphan disease afflicting just 20,000 patients in the seven main drug markets, found that there are only seventeen drugs under development in obstetrics, compared to six hundred sixty in cardiovascular disease and thirty-four in amyotrophic lateral sclerosis. *Id.* at 23–24. The authors of the study concluded that “[p]regnant women look set to miss out on the therapeutic advances expected from modern drug R&D in other fields that will benefit from combinatorial chemistry, high throughput screening, pharmacogenomics, bioinformatics, nanotechnology, the ‘-omic’ sciences, and biologics.” *Id.* at 25.

99. As of 2007, the only treatment for two of the three main pregnancy complications (intrauterine growth restriction and pre-eclampsia) was childbirth. Fisk & Atun, *supra* note 98, at 26. In the United States, there is no available approved treatment for the third (preterm labor), which is managed with drugs and other interventions of questionable efficacy. *Id.* See also Hyagriv N. Simhan & Steve N. Caritis, *Prevention of Preterm Delivery*, 357 NEW ENG. J. MED. 477, 479 (2009) (noting that “the whole class of labor-inhibiting drugs is largely ineffective”).

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can be sold.¹⁰⁰ To secure approval, firms must demonstrate to the FDA's satisfaction that their products "are safe and effective for their intended use."¹⁰¹ The FD&C Act requires that firms demonstrate safety and efficacy through "adequate and well-controlled investigations."¹⁰² This provides firms with a powerful incentive to do the investigation necessary to demonstrate to the satisfaction of the FDA that an experimental drug is safe and effective for one intended use.¹⁰³ They also have an incentive to do no more than necessary to secure approval, because delays in approval can lessen, and certainly forestall, the period of time during which they can sell their drug subject to patent-protected market exclusivity.¹⁰⁴

The Drug Price Competition and Patent Term Restoration Act of 1984 (commonly known as Hatch-Waxman) strengthens the incentive generated by the approval requirement by rewarding innovator firms with the exclusive right to use the data they submit to the FDA for five years.¹⁰⁵ For all practical purposes, this protects them from competition during that time.¹⁰⁶ Having to redo the research necessary to establish that a drug is safe and effective typically makes it cost-prohibitive for competitors to seek regulatory approval to market drugs still in the initial five-year data exclusivity period.¹⁰⁷

Like the patent regime, the incentive to develop information in order to secure marketing approval from the FDA fails to generate the information pregnant women need to make informed medication choices. The FDA requires as a condition of approval that drugs be tested to determine their potential to affect every stage of the reproductive process.¹⁰⁸ These tests are primarily conducted on rats;

100. 21 U.S.C.A. § 331(d) (West 2010).

101. Eisenberg, *supra* note 86, at 730.

102. 21 U.S.C.A. § 355(d) (West 2010).

103. Eisenberg, *supra* note 86, at 730. *See also* Adriane Fugh-Berman & Douglas Melnick, *Off-Label Promotion, On-Target Sales*, 5 PLOS MED. 1432, 1433 (2008) ("In development, drugs may be promising for several uses, and companies must choose one or two conditions on which to focus research. Ease of approval is the most important factor in this decision.").

104. Eisenberg, *supra* note 86, at 723 (explaining that firms are entitled to "patent term extensions of up to five years to compensate for some of the time that the patent meter is ticking pending regulatory approval of a new drug, so long as the total remaining patent life after extensions does not exceed fourteen years from the date of approval").

105. 21 U.S.C.A. § 355 (c)(3)(E)(ii) (West 2010).

106. Eisenberg, *supra* note 86, at 725, 730.

107. Once a drug's data exclusivity period has expired, a competitor no longer has to file a new drug application and show that its product is safe and effective. Instead, it can file an abbreviated new drug application (ANDA) based on a showing that the drug is bioequivalent to the already-approved drug. *Id.* at 727.

108. U.S. FOOD & DRUG ADMIN., DEPT. OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: M3(R2) NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS

tests to determine a drug's potential to adversely affect embryo-fetal development must usually be done on a second mammalian species as well, preferably rabbits.¹⁰⁹ Even tests done on well-studied mammals have a limited ability to predict human teratogenicity.¹¹⁰ Drug-associated abnormalities can occur in animals that do not occur in humans and vice versa.¹¹¹ For example, aspirin causes heart defects in animals but not in humans,¹¹² whereas the well-known human teratogen thalidomide caused no ill effects in animals.¹¹³ The rubella vaccine does not cross a pregnant monkey's placenta, whereas in humans it crosses the placenta and infects the fetus.¹¹⁴ Further complicating the analysis, drugs are tested in animals at doses which exceed the therapeutic dose in humans, and certain animal species have different baseline rates of birth defects.¹¹⁵

The FDA does not require sponsors to test their experimental drugs in pregnant women. In fact, under regulations and guidance promulgated by both the Department of Health & Human Services (HHS) and the FDA to protect the rights and interests of human research subjects, pregnancy is grounds for exclusion from most pre-approval clinical trials.

HHS' human subject research regulations apply to research conducted or supported by the agency, which encompasses the NIH among other

AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS 2 (2010), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073246.pdf> [hereinafter 2010 SAFETY STUDIES GUIDANCE].

109. U.S. FOOD & DRUG ADMIN., DEPT. OF HEALTH & HUMAN SERVS., GUIDANCE FOR INDUSTRY: DETECTION OF TOXICITY TO REPRODUCTION FOR MEDICINAL PRODUCTS 12-13 (1994), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074950.pdf>.

110. Wendy E. Wagner, *Choosing Ignorance in the Manufacture of Toxic Products*, 82 CORNELL L. REV. 773, 774 (1997) (noting the tentative relationship between a product's teratogenicity in animals and its teratogenicity in humans).

111. Content and Format of Labeling for Human Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,841 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

112. Koren et al., *supra* note 33, at 1131.

113. Bonnie Steinbock, *Ethical Issues Related to the Inclusion of Pregnant Women in Clinical Trials (II)*, in 2 WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 23, 23 (Anna C. Mastroianni et al. eds., 1994).

114. THE NAT'L COMM'N FOR THE PROT. OF HUMAN SUBJECTS OF BIOMEDICAL & BEHAVIORAL RES., U.S. DEP'T OF HEALTH, EDUCATION AND WELFARE, REPORT AND RECOMMENDATIONS: RESEARCH ON THE FETUS 12 (1975) ("Preliminary testing of rubella vaccine in monkeys indicated that the vaccine virus did not cross the placenta. In contrast, studies on women requesting therapeutic abortion showed clearly that the vaccine virus did indeed cross the placenta and infect the fetus, indicating the danger of administering the vaccine during pregnancy.")

115. Content and Format of Labeling for Human Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,841 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

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fundings.¹¹⁶ Beginning in 1991, when the HHS regulations were made applicable to research conducted or supported by most other federal agencies, they have been known as the “Common Rule.”¹¹⁷ The Common Rule references pregnant women several times, including them on a list of “vulnerable” subjects along with children, prisoners, handicapped or mentally disabled persons, and economically or educationally disadvantaged persons.¹¹⁸ The Rule provides that an Institutional Review Board (IRB) that regularly reviews research involving vulnerable subjects shall consider including on the IRB “one or more individuals who are knowledgeable about and experienced in working with these subjects.”¹¹⁹ The Rule also provides that, in fulfilling their duty to ensure that the selection of research subjects is equitable, IRBs “should be particularly cognizant of the special problems of research involving vulnerable populations,” and that pregnant women and other subjects “likely to be vulnerable to coercion or undue influence” should be provided with “additional safeguards” to protect their rights and welfare.¹²⁰ Finally, the Common Rule specifies that the informed consent form must include “[a] statement that the particular treatment or procedure may involve risks . . . to the embryo or fetus, if the subject is or may become pregnant[.]”¹²¹

Subpart B of Title 45 of the Code of Federal Regulations—the Common Rule is Subpart A—provides more specific guidance, setting forth “ten criteria that must be met if pregnant women are to be included in research protocols”¹²² Notably, Subpart B requires that, where scientifically appropriate, studies on pregnant animals and on non-pregnant women be conducted before pregnant women can be included in research.¹²³ In addition, a fetus may not be placed at risk unless there is a prospect for direct benefit to the woman or to the fetus, or unless the risk is minimal and “the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other

116. Carl H. Coleman, *Rationalizing Risk Assessment in Human Subject Research*, 46 ARIZ. L. REV. 1, 5 (2004).

117. *Id.*

118. See 45 C.F.R. §§ 46.107(a), 46.111(a)(3), (b), 46.116(b)(1) (2010). As Carl Coleman notes, the Common Rule does not define vulnerability and the examples it gives are diverse. Carl H. Coleman, *Vulnerability as a Regulatory Category in Human Subject Research*, 37 J.L. MED. & ETHICS 12, 12 (2009). With regard to pregnant women, “it is not clear why any special issues related to capacity or coercion would necessarily arise.” *Id.*

119. 45 C.F.R. § 46.107(a).

120. *Id.* § 46.111(a)(3), (b).

121. *Id.* § 46.116(b)(1).

122. Lyerly et al., *supra* note 14, at 18.

123. 45 C.F.R. § 46.204(a) (2010).

means.”¹²⁴ Subpart B also imposes unique informed consent requirements, providing that the woman’s consent to participate in research is sufficient if there is the possibility of benefit to her, or to her and the fetus, or if the risk is minimal and the research’s purpose is to develop important biomedical knowledge that cannot otherwise be obtained.¹²⁵ If there is a prospect of benefit to the fetus alone, however, both the mother and father must give consent, with exceptions made if the father “is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.”¹²⁶ Anne Drapkin Lyerly and her co-authors have opined that Subpart B’s ten requirements lead researchers to “side-step the questions and regulatory burden they represent by not including pregnant women” in clinical trials.¹²⁷

The FDA has not adopted Subpart B. In the late 1970s, however, in response to the diethylstilbestrol (DES) disaster, the agency recommended that rigorous pre-conditions be met before fertile women were included in the clinical trials it regulates, that is, those conducted in support of an application for approval of a new drug.¹²⁸ The FDA’s 1977 guideline “General Considerations for the Clinical Evaluation of

124. *Id.* § 46.204(d). In the context of pediatric research, the requirement that studies hold out the prospect of direct benefit has been interpreted broadly to include not just “[m]ost research on a drug to cure or alleviate the discomfort of a subject with an underlying disorder or condition” but also placebo-controlled trials in which some number of enrollees receive an inert intervention. I. Glenn Cohen, *Therapeutic Orphans, Pediatric Victims? The Best Pharmaceuticals for Children Act and Existing Human Subject Protections*, 58 FOOD & DRUG L.J. 661, 694–96 (2003). See also Sanjiv B. Amin et al., *Clinical Trials of Drugs Used Off-Label in Neonates: Ethical Issues and Alternative Study Designs*, 15 ACCOUNTABILITY IN RES. 168, 171–75 (2008) (discussing the ethical issues arising in active controlled and placebo controlled trials in neonates). Relying on evidence that even children who receive the placebo in placebo-controlled trials benefit from their participation, including from increased care and monitoring, the FDA has announced that placebo-controlled trials can be compatible with the direct benefit requirement. Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products, 66 Fed. Reg. 20,589, 20,593 (interim rule Apr. 24, 2001).

125. 45 C.F.R. § 46.204(d).

126. *Id.* § 46.204(e). Karen Rothenberg opines that:

It is incongruous that the paternal consent requirements in Subpart B have remained in place while DHHS regulations on research involving children only require the permission of one parent when such research poses either no greater than minimal risk or the prospect of direct benefit to the child. . . . Subpart B and its “special” treatment of pregnant women would become symbolic of the regulatory barriers to research that still remain.

Karen H. Rothenberg, *Gender Matters: Implications for Clinical Research and Women’s Health Care*, 32 HOUS. L. REV. 1201, 1229 (1996).

127. Lyerly et al., *supra* note 14, at 18.

128. L. Elizabeth Bowles, Note, *The Disfranchisement of Fertile Women in Clinical Trials: The Legal Ramifications of and Solutions for Rectifying the Knowledge Gap*, 45 VAND. L. REV. 877, 895–96 (1992).

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Drugs,” recommended that “[f]emales who are pregnant, or are at risk of becoming pregnant, should be excluded” from Phase I clinical trials, which include “the initial introduction of a drug into man.”¹²⁹ Phase I trials can consist of drug dynamic and metabolic studies, toxicity and pharmacologic effect studies on healthy research participants, and dose-ranging studies on patients to evaluate safety and possibly provide early evidence of effectiveness.¹³⁰ They typically involve twenty to eighty participants.¹³¹ The guideline specified that all premenopausal women who were “capable of becoming pregnant” were “women of childbearing potential” and should be excluded, even if they were single, used contraception, or were married to men who were vasectomized or who used contraception.¹³² Women in certain institutions, for example prison, might not be “of childbearing potential,” but women in others, for example mental institutions, would be.¹³³

Women of childbearing potential could be included in Phase II trials, defined as “controlled trials designed to demonstrate effectiveness and relative safety” including approximately one hundred to two hundred participants, but only if earlier Phase II trials had already produced “adequate information on efficacy and relative safety” and certain recommended animal reproductive studies were complete; they could not be included in Phase III trials, defined as expanded controlled and uncontrolled trials designed to elicit additional evidence of safety and efficacy, until all of the recommended animal reproductive studies were complete.¹³⁴ The FDA only allowed for exceptions to the animal reproductive studies requirement where the investigative drug could be life-saving or life-prolonging, where the drug belonged to a class whose teratogenic potential was known, or where the woman was “institutionalized for a time period adequate to establish a non-pregnant state.”¹³⁵ In these cases, the agency recommended that women be pregnancy tested before taking the drug and that they be given advice about appropriate contraceptives.¹³⁶

In the 1980s and early 1990s, attitudes towards clinical research

129. U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS 7 (1977). Later in the document, the FDA qualifies its advice, saying that women of childbearing potential should be excluded from Phase I clinical trials “[i]n most cases,” *id.* at 7, and “in general,” *id.* at 10.

130. *Id.* at 6.

131. *Id.*

132. *Id.* at 10.

133. *Id.*

134. *Id.* at 6, 10.

135. *Id.* at 10.

136. *Id.* at 11.

shifted. Women's health advocates argued that the government and clinical research establishment were harming women rather than helping them by excluding them, pregnant or not, from research.¹³⁷ In 1986, the National Institutes of Health (NIH) adopted a new policy encouraging grant applicants to include women in their research plans.¹³⁸ In 1990, in response to a Government Accounting Office (GAO) finding that the policy adopted in 1986 had yet to be fully implemented,¹³⁹ the NIH revised its approach. Grant applicants were required to include women unless there was a "compelling justification" for exclusion. One example of a compelling justification was that the research posed an "unacceptable risk for women of childbearing age."¹⁴⁰ Also in 1990, the NIH for the first time required its own researchers to include women in the absence of a "clear rationale" for exclusion.¹⁴¹ Exclusion was justified under the policy when the research to be conducted could "expose the fetus to undue risks."¹⁴²

In 1993, Congress stepped in, passing the National Institutes of Health Revitalization Act, which required that women be included in federally funded clinical studies unless their health or the purpose of the research made their inclusion inappropriate; cost was not an acceptable reason for exclusion.¹⁴³ The Act also required that federally funded Phase III trials be designed to allow for the analysis of gender-linked differences.¹⁴⁴ The NIH conformed its policy to the legislation, promulgating new Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research in 1994.¹⁴⁵ For women of childbearing potential, a presumption of inclusion in federally funded clinical trials was now the law. The inclusion of pregnant women was still conditioned on meeting Subpart B's ten criteria, however.

In 1994, the Institute of Medicine (IOM) issued *Women and Health Research*, a report written at the request of the NIH Office of Research

137. Christine Grady & Colleen Denny, *Research Involving Women*, in THE OXFORD TEXTBOOK OF RESEARCH ETHICS 407, 409 (Ezekiel J. Emanuel et al. eds., 2008).

138. *Id.*

139. *National Institutes of Health: Problems in Implementing Policy on Women in Study Populations, Testimony Before the Subcomm. on Health and the Environment, Comm. on Energy and Commerce*, 101st Cong. 3-4 (1990) (statement of Mark Nadel, Associate Director, National and Public Health Issues, Human Resource division), available at <http://archive.gao.gov/d48t13/141859.pdf>.

140. Karen H. Rothenberg, *Gender Matters: Implications for Clinical Research and Women's Health Care*, 32 HOUS. L. REV. 1201, 1231 (1996).

141. *Id.*

142. *Id.*

143. *Id.* at 142.

144. Grady & Denny, *supra* note 137, at 410.

145. NIH Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research, 59 Fed. Reg. 11,146 (Mar. 9, 1994).

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on Women's Health, which recommended that Subpart B be revised and reissued to reflect a presumption of inclusion of pregnant women in clinical trials.¹⁴⁶ The IOM Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies concluded that:

It is the responsibility of investigators and IRBs to ensure that pregnant women are provided with adequate information about the risks and benefits to themselves, their pregnancies and their potential offspring. Even when evidence concerning risks is unknown or ambiguous, the decision about acceptability of risk to the pregnancy or to offspring should be made by the woman as part of the informed consent process.¹⁴⁷

Most of the members of the Committee recommended in addition that pregnant women not be excluded unless the IRB issued written findings that “(1) there is no prospect of medical benefit to the pregnant woman, and (2) a risk of significant harm to potential offspring is known or can plausibly be inferred.”¹⁴⁸

Neither HHS nor the FDA adopted the IOM's recommendations. When the FDA revised its guidelines on the inclusion of women in clinical trials, after a GAO audit requested by the Congressional Caucus for Women's Issues in 1992 found that women were underrepresented in new drug research, the agency continued to recommend that pregnant women be categorically excluded from clinical trials of new drugs.¹⁴⁹ The revised guidelines focus on ways to include women of childbearing potential in trials without inadvertently exposing fetuses to potentially toxic drugs.¹⁵⁰ They provide that “[i]n general, it is expected that reproductive toxicity studies will be completed before there is large-scale exposure of women of child-bearing potential, i.e., usually by the end of phase 2 and before any expanded access program is implemented.”¹⁵¹ The FDA goes on to recommend that clinical protocols include measures designed to minimize the possibility of fetal exposure to investigational drugs, including use of the informed consent process, pregnancy testing, and contraception, unless the purpose of a trial is to study a drug's effects during pregnancy.¹⁵² Today, researchers

146. 1 COMM. ON ETHICAL & LEGAL ISSUES RELATING TO THE INCLUSION OF WOMEN IN CLINICAL STUDIES, INST. OF MED., *WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES* 194–95 (Anna C. Mastroianni et al. eds., 1994) [hereinafter INST. OF MED.].

147. *Id.* at 195.

148. *Id.* at 198.

149. Rothenberg, *supra* note 126, at 1239.

150. Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, 58 Fed. Reg. 39,406, 39,409–11 (July 22, 1993).

151. *Id.* at 39,411.

152. *Id.*

frequently ask women of childbearing age to agree to use birth control as a condition of trial participation.¹⁵³ Sometimes, women are required to use two methods of birth control, even though research shows that, at least in some populations, this approach fails to reduce pregnancy rates.¹⁵⁴

In a guidance document on nonclinical safety studies released in January 2010, the FDA suggests that pregnant women need not always be excluded from clinical trials.¹⁵⁵ In it, the agency states that pregnant women may be included after “all female reproduction toxicity studies . . . and the standard battery of genotoxicity tests” are completed and “safety data from previous human exposure [has been] evaluated.”¹⁵⁶

In sum, the FDA does not require that experimental drugs be tested in pregnant women as a condition of approval. Rather, the agency has actively discouraged such testing under most circumstances. The HHS regulations are also restrictive. This is one reason why, although women now constitute more than half of the population of research participants,¹⁵⁷ “many researchers and institutional review boards (IRBs) continue to regard pregnancy as a near-automatic cause for exclusion”¹⁵⁸

This is not to suggest that experimental drugs should without exception be tested in pregnant women as a condition of approval or that if they were it would close the information gap. It may more often than not prove impossible to conduct pre-approval testing in pregnant women in a scientifically sound and ethical manner. If only a small number of pregnant women are included in a given trial, the researchers may not be able to draw statistically valid conclusions about the experimental drug’s

153. See, e.g., Stanford University Research Compliance Office, Stanford Consent Form Template with HIPAA 5, available at http://humansubjects.stanford.edu/research/medical/med_consent.html#forms (last visited Nov. 12, 2010) (suggesting that informed consent forms incorporate the following language: “If you are a woman who is able to get pregnant, it is expected that you will use an effective method of birth control to prevent exposing a fetus to a potentially dangerous agent with unknown risk. If you are pregnant or currently breast feeding, you may not participate in this study.”).

154. E-mail from Anne Drapkin Lyerly, Associate Professor of Obstetrics & Gynecology, Duke Univ. Sch. of Med., to Kate Greenwood, Research Fellow and Lecturer in Law, Seton Hall Univ. Sch. of Law (July 30, 2009, 11:49 EST) (on file with author).

155. 2010 SAFETY STUDIES GUIDANCE, *supra* note 108, at 18–19.

156. *Id.*

157. U. S. GEN. ACCOUNTING OFFICE, GAO-01-754, WOMEN’S HEALTH: WOMEN SUFFICIENTLY REPRESENTED IN NEW DRUG TESTING, BUT FDA OVERSIGHT NEEDS IMPROVEMENT 3 (2001).

158. Lyerly et al., *supra* note 14, at 6. See also Diego F. Wyszynski, *Pregnancy Exposure Registries: Academic Opportunities and Industry Responsibility*, 85 BIRTH DEFECTS RES. PART A: CLINICAL & MOLECULAR TERATOLOGY 93, 93 (2009) (“[P]regnant women are actively excluded from clinical trials[.]”).

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safety and efficacy during pregnancy. This could mean that the risks taken by the women and their fetuses outweigh the benefits of including them. Even clinical trials done exclusively on pregnant women are frequently too small to allow for statistically sound conclusions about rare birth defects.¹⁵⁹ Most human reproductive studies have fewer than 300 participants.¹⁶⁰ Given the baseline birth defect incidence of 3%, a study of that size can rule out the possibility that a drug more than doubles the risk of birth defects, but it will not be able to detect smaller increases in risk.¹⁶¹ Most women would consider smaller increases significant. Cigarette smoking, for example, is associated with less than a doubling of the risk of birth defects.¹⁶² Moreover, while clinical trials “focus on immediate adverse effects,”¹⁶³ pregnant women are equally concerned about the long-term effects of in utero exposure to drugs on their children’s growth and development. In the end, epidemiological studies may be the only way to generate information about both rare birth defects and long-term effects. However, such studies cannot be done before a drug is approved and marketed.

C. Research Required for Permission to Make Marketing Claims About a Prescription Drug

After a drug is approved, it is subject to a set of statutory and regulatory provisions that incentivize its manufacturer to continue developing information about its safety and efficacy. First, the FD&C Act requires that on-label marketing claims be well-supported. An advertisement violates the Act if it includes a representation or suggestion, for example that one drug is better or safer than another drug, that has not been demonstrated by either substantial evidence or substantial clinical experience.¹⁶⁴ If a manufacturer wishes to make certain claims it must be able to point to research that supports them; if such research does not exist, the manufacturer has an incentive to conduct it. Second, when the FDA grants permission to sell a prescription drug, it does so for an indicated use or uses and subject to

159. Comments of Pharm. Res. and Mfrs. of Am. on Content and Format of Labeling for Human Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831 (May 29, 2008).

160. Comments of Public Citizen on Content and Format of Labeling for Human Prescription Drugs and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831 (May 29, 2008).

161. *Id.*

162. *Id.*

163. Lo & Friedman, *supra* note 71, at 465.

164. 21 C.F.R. § 202.1(e)(6)(i) (2010).

the terms and conditions specified in the approved label.¹⁶⁵ While physicians are free to prescribe the drug for any purpose or in any manner they deem appropriate, the FD&C Act prohibits the manufacturer from promoting the drug except in accord with its agency-approved label.¹⁶⁶ This ban on off-label promotion creates an incentive for manufacturers to conduct the research needed to support a supplemental new drug application to move off-label doses, indications, methods of administration, or patient populations on-label. Finally, Hatch-Waxman rewards manufacturers who submit successful supplemental new drug applications with a supplemental period of data exclusivity.

Under Hatch-Waxman, if a company submits a supplemental new drug application supported by “new clinical investigations” and the FDA approves the application, the company is rewarded with three additional years of data exclusivity.¹⁶⁷ If the initial five-year data exclusivity period has expired, competitors are not barred from relying on the data submitted in support of the original indication in seeking approval to manufacture a generic version of the drug.¹⁶⁸ While a generic manufacturer cannot promote the drug for the use that is protected by the three additional years of data exclusivity, doctors are free to prescribe the generic version for either the original or the newly approved use. This weakens the incentive Hatch-Waxman gives to innovator firms to conduct the research necessary to support a supplemental new drug application.

The ban on off-label promotion provides firms with an additional push “to go through the strict FDA preclinical and clinical trial process to get off-label uses on-label.”¹⁶⁹ If a company wishes to promote a drug for a previously unapproved use, it must conduct the clinical investigations necessary to establish the drug’s safety and efficacy for that use and then submit a supplemental new drug application to the FDA. Supplemental new drug applications are required any time a company wishes to make a “major” change to a drug’s label.¹⁷⁰ This could include an additional indication as well as a change in dose,

165. Rebecca Dresser & Joel Frader, *Off-Label Prescribing: A Call for Heightened Professional and Government Oversight*, 37 J.L. MED. & ETHICS 476, 477 (2009).

166. Wash. Legal Found. v. Friedman, 13 F. Supp. 2d 51, 55–56 (D.D.C. 1998), *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999), *vacated in part by* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000).

167. 21 U.S.C.A. § 355(c)(3)(E)(iii) (West 2010).

168. Eisenberg, *supra* note 86, at 729.

169. Friedman, 13 F. Supp. 2d at 70–71 (D.D.C. 1998).

170. 21 C.F.R. § 314.70(b) (2010).

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method of administration, or patient population.¹⁷¹

The FDA frequently disavows jurisdiction over the practice of medicine. It has noted that “unapproved ‘or more precisely, unlabeled’ uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature.”¹⁷² In the device context, the FD&C Act states that “nothing in this chapter shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship,” and the Supreme Court has held that off-label use “is an accepted and necessary corollary of the FDA’s mission to regulate in this area without directly interfering with the practice of medicine.”¹⁷³

While off-label use is permitted, off-label promotion is not.¹⁷⁴ First, the FD&C Act bans the sale of unapproved “new drug[s,]”¹⁷⁵ and when an approved drug is marketed for an unapproved use, the FDA’s position is that the drug becomes “an unapproved new drug with respect to that use.”¹⁷⁶ The agency reasons that the Act’s definition of “new drug” includes any drug that the FDA has not determined to be “safe and effective for use under the conditions prescribed, recommended, or suggested in [its] labeling.”¹⁷⁷ Labeling, in turn, is defined to include “all labels and other written, printed, or graphic matters” on the drug itself, on the drug’s “containers or wrappers,” or that accompany the drug.¹⁷⁸ The Supreme Court has held that written matters “accompany” a drug when they “supplement[] or explain[] it, in the manner that a committee report of the Congress accompanies a bill. No physical attachment one to the other is necessary. It is the textual relationship

171. *Ass’n of Am. Physicians & Surgeons, Inc. v. FDA*, 226 F. Supp. 2d 204, 206 (D.D.C. 2002).

172. Citizen Petition Regarding the Food and Drug Administration’s Policy on Promotion of Unapproved Uses of Approved Drugs and Devices; Request for Comments, 59 Fed. Reg. 59,820, 59,821 (Nov. 18, 1994).

173. *Buckman Co. v. Plaintiffs’ Legal Comm.*, 531 U.S. 341, 350 (2001) (citing 21 U.S.C. § 396 (1994 & Supp. V)).

174. The FDA does allow certain company communications about off-label uses. For example, companies can distribute, among other things, peer-reviewed medical journal articles that discuss such uses. See U.S. FOOD & DRUG ADMIN., DEPT. OF HEALTH & HUMAN SERVS., 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/RegulatoryInformation/Guidances/ucm125126.htm>.

175. 21 U.S.C.A. §§ 331(d), 355(a) (West 2010).

176. U.S. FOOD & DRUG ADMIN., *supra* note 174.

177. 21 U.S.C.A. § 321(p) (West 2010).

178. § 321(m). *But cf.* § 321(k) (defining “label” more narrowly, to include “a display of written, printed, or graphic matter upon the immediate container of any article”).

that is significant.”¹⁷⁹ Whenever a company makes promotional claims in writing about an unapproved use of a drug, then, the drug becomes a “new drug” for purposes of that use, which makes it illegal to sell the drug for that use under the FD&C Act.

Off-label promotion is prohibited for a second reason. When a company promotes its drug for an off-label use the drug becomes “misbranded” and therefore banned for sale under the Act.¹⁸⁰ The Act requires that labeling contain “adequate directions” for “intended” uses.¹⁸¹ FDA regulations require that a prescription drug’s labeling include

adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended, including all purposes for which it is advertised or represented[.]¹⁸²

Intent is defined objectively, with reference to, for example, “labeling claims, advertising matter, or oral or written statements by such persons or their representatives.”¹⁸³ A company’s promotional claims about an unapproved use demonstrate that the use is “intended;” because the label lacks adequate directions for the use, the drug is misbranded and banned for sale.

A number of factors are considered by companies when deciding whether to file a supplemental new drug application. A key factor is the projected increase in sales obtaining such approval would generate. Sales could increase for a variety of reasons. The fact of the FDA’s approval could have a positive effect on perceptions of the drug, or the addition of new information to the label could bring it to the attention of new health care providers and patients. New indications can have halo effects. If a painkiller is approved to treat one particularly painful condition, physicians and patients might believe that it is efficacious for other such conditions. Most observers agree that the central advantage to adding a new use to the label is that it allows the manufacturer to promote the drug for that use.¹⁸⁴

179. *Kordel v. United States*, 335 U.S. 345, 350 (1948).

180. U.S. FOOD & DRUG ADMIN., *supra* note 174 (citing 21 U.S.C. § 352(f); 21 C.F.R. § 201.100(c)(1)).

181. 21 U.S.C.A. § 352(f)(1) (West 2010).

182. 21 C.F.R. § 201.100(c)(1) (2010).

183. *Id.* § 201.128.

184. *See, e.g., Wash. Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 70 (D.D.C. 1998) (holding that “defendants have proved to this court’s satisfaction that dissemination of scientific information on

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In addition to direct-to-consumer advertising, promotion includes physician detailing, both the traditional visits by sales representatives to doctors' offices and newer online approaches.¹⁸⁵ Companies also promote their products by engaging physicians to give promotional talks to their fellow doctors¹⁸⁶ and by running advertisements targeting physicians in medical journals, on the internet, and elsewhere.¹⁸⁷ Promotion to health insurance companies, managed care organizations, and pharmaceutical benefit management firms is also prevalent.¹⁸⁸

The authors of a recently published meta-analysis of fifty-eight studies concluded that “promotional expenditures have a significant and positive effect on sales in pharmaceutical markets,” but that “the elasticities of promotional expenditures are modest in size[.]”¹⁸⁹ Physician detailing is the most effective form of promotion in most markets, followed by direct-to-physician advertising.¹⁹⁰ Demonstrated effectiveness aside, the amounts pharmaceutical firms spend on promotion suggest that they have concluded it is effective, which in turn suggests that they would view permission to promote positively. IMS Health, self-described as “the world’s leading provider of market

off-label uses is an effective means of influencing physicians to prescribe a drug for a given condition. . . . Consequently, the dissemination of information demonstrating that a drug is effective has a positive effect upon sales of the drug.” (citations omitted), *amended by* 36 F. Supp. 2d 16 (D.D.C. 1999), *vacated in part by* Wash. Legal Found. v. Henney, 202 F.3d 331 (D.C. Cir. 2000); Catherine Larkin, *Lilly Wins Backing to Use Antidepressant Cymbalta for Back, Arthritis Pain*, BLOOMBERG, Nov. 4, 2010, <http://www.bloomberg.com/news/2010-11-04/lilly-wins-backing-to-use-antidepressant-cymbalta-for-back-arthritis-pain.html> (citing an analyst’s estimate that the approval of a supplemental new drug application for the antidepressant Cymbalta will result in a \$500 million increase in annual sales).

185. Marc Iskowitz, *Pfizer Nearly Doubles Amount Spent on E-Detailing*, MMM-ONLINE, Jan. 19, 2010, <http://www.mmm-online.com/pfizer-nearly-doubles-amount-spent-on-e-detailing/article/161727/>.

186. See PHARM. RES. & MFRS. OF AM., CODE ON INTERACTIONS WITH HEALTHCARE PROFESSIONALS 9–10 (2008) (setting forth ethical guidelines for company-run “Speaker Programs and Speaker Training Meetings”).

187. See Puneet Manchanda & Elisabeth Honka, *The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review*, 5 YALE J. HEALTH POL’Y L. & ETHICS 785, 785–86 (2005) (“The marketing efforts directed at physicians comprise personal selling through sales representatives (detailing); sampling (provision of drugs at no cost); physician meetings and events; and advertisements in medical journals.” (citations omitted)); Running a Hospital, <http://runningahospital.blogspot.com/2009/05/3-1-1-0.html> (May 26, 2009, 06:37 PM) (questioning the efficacy of an advertisement for an atrial fibrillation catheter that appeared on plastic bags handed out by airport security; commenters noted that the distribution of the bags coincided with a meeting of the Heart Rhythm Society).

188. John E. Calfee et al., *Direct-to-Consumer Advertising and the Demand for Cholesterol-Reducing Drugs*, 45 J.L. & ECON. 673, 678 (2002).

189. Sara T.M. Kremer et al., *Generalizations on the Effectiveness of Pharmaceutical Promotional Expenditures*, 25 INT’L J. RES. MKTG. 234, 244 (2008).

190. *Id.*

intelligence to the pharmaceutical and healthcare industries,”¹⁹¹ estimates that in 2009 companies spent \$4.34 billion on direct-to-consumer advertising, \$6.29 billion on sales representative detailing, and \$315 million on medical journal advertising, for a total United States promotional spend of \$ 1.09 billion.¹⁹²

In addition to whether a supplemental new drug application will lead to increased sales, companies must also consider whether, as a scientific matter, they will be able to support the new indication or other additions to the label they hope to make. They must also consider the cost of mounting the necessary clinical trials and the risk that the trial results might be negative and cause their consumer base to shrink rather than expand.¹⁹³ There is no expectation or requirement that companies factor public health priorities into their calculus.

Like the initial approval requirement, both the requirement that promotional claims be well-supported and the supplemental approval requirement are of limited benefit to pregnant women. First, the fact that the additional period of exclusivity is only granted to manufacturers if they present the results of a “new clinical investigation” limits the value of the incentive for pregnant women. Epidemiological studies may be as valuable as or more valuable than clinical trials as a route to expanding our knowledge of maternal–fetal pharmacology, particularly with regard to safety information. More fundamentally, for most drugs, permission to freely promote them to a small, transient patient population like pregnant women is unlikely to be enticing to companies. Analogously, prior to the enactment of legislation establishing special incentives for pediatric labeling changes, companies declined to test their products on children and were content to let the labels reflect the lack of pediatric safety or efficacy information.¹⁹⁴ Finally, a pregnancy section that reflects the fact that a drug is unstudied in pregnant women is less of a handicap than it might be because most drugs are similarly unstudied. For example, in a case brought against GlaxoSmithKline

191. IMS, IMS Facts at a Glance, <http://www.imshealth.com/portal/site/imshealth/menuitem> (follow “About Us . . . more” hyperlink; then follow “Facts-At-a-Glance” hyperlink) (last visited Feb. 25, 2010).

192. IMS, Total U.S. Promotional Spend by Type, 2009, http://www.imshealth.com/deployedfiles/imshealth/Global/Content/StaticFile/Top_Line_Data/PromoUpdate2009.pdf (last visited Nov. 8, 2010).

193. See Leslie Kushner, Note, *Incentivizing Postmarketing Pharmaceutical Product Safety Testing with Extension of Exclusivity Periods*, 19 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 519, 537–39 (2009) (discussing impact of safety findings on sales of the anemia drug Aranesp and the multiple sclerosis drug Tysabri).

194. Lauren Hammer Breslow, Note, *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, 152–53 (2002).

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alleging that its anti-depressant Paxil caused birth defects, witnesses for the plaintiff testified at trial that GSK sales representatives exhorted physicians to prescribe Paxil on the grounds that (1) at that time, it was in category C¹⁹⁵ and (2) no drug in its class had been shown to be safer in pregnancy.¹⁹⁶

D. Research Required by Products Liability Law

Companies' potential exposure to tort liability also influences their decisions to conduct clinical trials or otherwise develop information about their drugs when used during pregnancy. First, companies have an incentive to study their drugs to the extent that early detection of safety issues reduces the number of injuries caused by a drug and, concomitantly, reduces a company's exposure to damage awards. Many argue, albeit with the benefit of hindsight, that the manufacturers of the well-known teratogens DES and thalidomide increased their liability exposure by inadequately testing their drugs. Second, the tort system incentivizes companies to study their drugs because they can be liable for failure to warn of risks for which they did not test. The Paxil case, *Kilker v. SmithKline Beecham*, is an example of this. In October 2009, the jury found that GSK was negligent, albeit not grossly so, for failing to warn of an association between Paxil and certain cardiac birth defects.¹⁹⁷ The jury awarded the plaintiff \$2.5 million¹⁹⁸ and GSK subsequently agreed to pay more than \$1 billion to settle over 800 additional cases.¹⁹⁹ On the other hand, the tort system negatively incentivizes companies, because they are exposed to liability for harms incurred by research participants and because they are often sued when adverse research results are announced regardless of whether they acted responsibly. GSK may view the Paxil case as an example of the latter

195. Transcript of Testimony of David Healy at 20, *Kilker v. SmithKline Beecham Corp.* (Pa. Ct. Com. Pl. Sept. 16, 2009 Morning Session) (No. 1813) (attorney for the plaintiff Sean Patrick Tracey representing to the court that "Dr. Ruppertsberger has testified that the GSK sales reps came to his office and pushed him to prescribe this drug to women of childbearing age because it was a Category C").

196. Transcript of Testimony of Suzanne Parisian at 31–32, *Kilker v. SmithKline Beecham Corp.* (Pa. Ct. Com. Pl. Sept. 18, 2009 Afternoon Session) (No. 1813) (reviewing a memorandum for sales representatives and affirming that "[i]t says study, reinforce what you have already been telling physicians. No SSRI has been shown to have superior safety versus Paxil for use during pregnancy[.]").

197. Jef Feeley & Sophia Pearson, *Glaxo Ordered to Pay \$2.5 Million for Paxil Defects (Update4)*, BLOOMBERG, Oct. 13, 2009, <http://www.bloomberg.com/apps/news?pid=20601103&sid=apENrx2KUBcY>.

198. *Id.*

199. Jef Feeley & Trista Kelley, *Glaxo Said to Have Paid \$1 Billion Over Paxil Suits*, BLOOMBERG, July 20, 2010, <http://www.bloomberg.com/news/2010-07-20/glaxo-said-to-have-paid-1-billion-to-resolve-paxil-birth-defect-lawsuits.html>.

phenomenon. In this subpart, I elaborate on the above incentives and conclude that it is impossible to precisely calibrate and weigh them against one another to determine whether the tort system, on balance, incentivizes or disincentivizes research. I then discuss reasons why research studying the effects of drugs on pregnant women and fetuses might be especially susceptible to a liability barrier.

To the extent that research reveals a drug's potential to cause harm before the drug causes actual harm, the company that conducted the research will be rewarded for doing so in the form of reduced exposure to liability. In a commissioned paper accompanying the IOM's 1994 report *Women and Health Research*, Ellen Wright Clayton predicted that pharmaceutical manufacturers' "potential for liability is much greater if efforts are not made to detect fetotoxic effects."²⁰⁰ She argued that if a drug with unknown but knowable fetotoxic effects were to enter the marketplace and be widely used before those effects were discovered, many children would be harmed and their lawyers would argue that the manufacturer had a duty to discover the drug's ill effects.²⁰¹ Clayton contrasts this scenario with a manufacturer who studies its drug prior to marketing and discovers its fetotoxic effects at an early stage. She notes that "the risk of incurring liability during the early stages of drug investigation is actually quite small" and that a manufacturer who is aware of a drug's fetotoxicity can "transfer the risk of liability to the health care provider under the learned intermediary doctrine."²⁰²

An argument can be made that the three drugs most often cited as evidence of a liability barrier to researching the safety and efficacy of drugs when used during pregnancy—thalidomide, DES, and Bendectin—in fact support Clayton's position. In all three cases, the manufacturer or manufacturers' liability would have been reduced had they researched their products' teratogenicity before marketing them.²⁰³ Bendectin is an especially interesting case study. The drug was prescribed to more than thirty-three million pregnant women to treat pregnancy-induced nausea and vomiting between 1956, when it was introduced, and 1983, when its manufacturer, Merrell Dow, withdrew it

200. Ellen Wright Clayton, *Liability Exposure When Offspring Are Injured Because of Their Parents' Participation in Clinical Trials*, in 2 *WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES* 108 (Anna C. Mastroianni et al. eds., 1994).

201. *Id.* at 109.

202. *Id.* at 103, 109. Adopted by almost all jurisdictions, the learned intermediary doctrine provides that manufacturers are not obliged to warn patients directly; giving an adequate warning to the physicians who prescribe the drug suffices. See Margaret Gilhooley, *Learned Intermediaries, Prescription Drugs, and Patient Information*, 30 *ST. LOUIS U. L.J.* 633, 634 (1985).

203. Edward J. Saunders & Jeanne A. Saunders, *Drug Therapy in Pregnancy: The Lessons of Diethylstilbestrol, Thalidomide, and Bendectin*, 11 *HEALTH CARE FOR WOMEN INT'L* 423, 423 (1990).

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from the United States market citing the large and increasing number of lawsuits alleging that the drug caused birth defects.²⁰⁴ At its peak, Bendectin was prescribed to up to 40% of pregnant women.²⁰⁵

Despite the fact that Bendectin was indicated for use during pregnancy and was in fact used by millions of pregnant women, Merrell Dow did not test its ingredients for reproductive toxicity prior to marketing.²⁰⁶ The FDA did not require such tests at the time, and each of the drug's three ingredients was prescribed singly without recorded adverse effects.²⁰⁷ Merrell Dow's decision not to test Bendectin did not result in fetal harm; multiple large, high-quality epidemiological studies have found no causal relationship between the drug and birth defects.²⁰⁸ Wendy Wagner contends that the reason some Bendectin plaintiffs nevertheless prevailed was at least in part because of Merrell Dow's failure to engage in information development, namely its failure to test Bendectin's long-term safety and its prior failure to test adequately MER/29 and thalidomide, products which caused severe harm.²⁰⁹ The plaintiffs' evidence of these failures was "largely un rebutted."²¹⁰ Joseph Sanders' review of multiple trial transcripts showed that the Bendectin plaintiffs commingled the relatively strong evidence that Merrell Dow's testing and marketing of the drug was negligent with the relatively weak evidence that the drug caused harm.²¹¹ A survey of several jurors in a case in which a Bendectin plaintiff won large compensatory and punitive damage awards revealed that the plaintiffs' strategy was effective; the jurors spent more time on the evidence of Merrell Dow's scientific misconduct than on any other evidence.²¹²

The tort system also rewards companies for studying their drugs because by doing so they reduce the chance that they will be found liable for failure to warn of risks for which they failed to test. Failure-to-test prescription drug claims are typically brought under the rubric of failure to warn of an unknown but knowable risk. The Restatement (Third) of Torts provides as follows:

A prescription drug or medical device is not reasonably safe due to

204. Jane E. Brody, *Shadow of Doubt Wipes Out Bendectin*, N.Y. TIMES, June 19, 1983, at E7.

205. Koren et al., *supra* note 33, at 1129.

206. Joseph Sanders, *The Bendectin Litigation: A Case Study in the Life Cycle of Mass Torts*, 43 HASTINGS L.J. 301, 321 (1992).

207. *Id.* at 317, 321.

208. Joseph Sanders, *From Science to Evidence: The Testimony on Causation in the Bendectin Cases*, 46 STAN. L. REV. 1, 7 (1993).

209. Wagner, *supra* note 110, at 829–30.

210. *Id.*

211. *Id.*

212. *Id.*

inadequate instructions or warnings if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to: (1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings; or (2) the patient when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings.²¹³

The Restatement provides that drug “manufacturers have the responsibility to perform reasonable testing prior to marketing a product and to discover risks and risk-avoidance measures that such testing would reveal.”²¹⁴ After marketing a product, companies have a continuous duty “to keep abreast of the current state of knowledge . . . as gained through research, adverse reaction reports, scientific literature, and other available methods.”²¹⁵

It is not clear from the case law to what extent companies must engage in independent testing once a product is on the market.²¹⁶ In the Paxil case, the plaintiff successfully argued that GSK was negligent because it (1) failed to conduct additional animal testing, beyond what the FDA required, to determine why Paxil had the effects that it did on the animals studied, and (2) failed to warn doctors of Paxil’s risks once the company began receiving adverse event reports of birth defects.²¹⁷ In *Horne v. Novartis Pharmaceuticals*, by contrast, the District Court for the Western District of North Carolina granted the defendant manufacturer’s motion to dismiss the plaintiff’s failure to warn claim, finding that the plaintiff’s claim was preempted in part because she failed to allege that:

at the time of her pregnancy, the Defendant possessed any studies revealing birth defects associated with the first trimester use of Lotensin HCT® in particular or ACE inhibitors in general. Nor has the Plaintiff

213. RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6(d) (1998). Many medications are used “off-label” in pregnant women, for example nifedipine, an anti-hypertensive drug, and terbutaline, an anti-asthmatic drug, both of which are prescribed to arrest pre-term labor. Courts have held that manufacturers are liable for failure to warn of known risks attendant to off-label uses if the uses are reasonably foreseeable. See *Knipe v. Smithkline Beecham*, 583 F. Supp. 2d 602, 629 (E.D. Pa. 2008) (citing cases).

214. RESTATEMENT (THIRD) OF TORTS: PRODUCTS LIABILITY § 6 cmt. g (1998). See also *id.* § 10 cmt. c (charging sellers with “knowledge of what reasonable testing would reveal” and noting that “courts traditionally impose a continuing duty of reasonable care to test and monitor after sale to discover product-related risks.”).

215. *Lindsay v. Ortho Pharm. Corp.*, 637 F.2d 87, 91 (2d Cir. 1980).

216. Lars Noah, *This is Your Products Liability Restatement on Drugs*, 74 BROOK. L. REV. 839, 907 (2009).

217. Transcript of Opening Statement of Sean Patrick Tracey at 31–32, 49–50, *Kilker v. SmithKline Beecham Corp.* (Pa. Ct. Com. Pl. Sept. 15, 2009) (No. 1813).

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alleged that the Defendant had any “reasonable evidence” of such a causal association at the time of her pregnancy which would have required the revision of the labeling[.]²¹⁸

Clearly, products liability law gives companies a strong incentive to stay abreast of third-party research, and to make immediate changes to product warnings as science advances. Their incentive to advance the science themselves is weaker.²¹⁹ As the Paxil verdict shows, however, there is a real risk that a jury will find a company’s choice not to study its product unreasonable.

Many believe that any reduction in exposure to failure-to-warn liability from information development is outweighed by its exposure-increasing effects and that there is in fact a liability barrier that is responsible for the slow pace of information development.²²⁰ For one, drug companies and others involved in clinical research have been sued when participants in clinical trials sustained injury.²²¹ In cases in which

218. *Horne v. Novartis Pharms. Corp.*, 541 F. Supp. 2d 768, 782–83 (W.D.N.C. 2008) (internal citation omitted).

219. George Conk and others have argued that, whatever its precise contours, the tort law duty to test approved products for safety issues is inadequate. See Lars Noah, *Platitudes about “Product Stewardship” in Torts: Continuing Drug Research and Education*, 15 MICH. TELECOMM. & TECH. L. REV. 359, 360 (2009) (citing George W. Conk, *Punctuated Equilibrium: Why § 402A Flourished and the Products Liability Restatement Languished*, 26 REV. LITIG. 799, 856–62, 878–80 (2007); Margaret A. Berger & Aaron D. Twerski, *Uncertainty and Informed Choice: Unmasking Daubert*, 104 MICH. L. REV. 257 (2005)). Conk believes that companies have or should have a duty of “product stewardship” which flows “from the manufacturer’s design experience and from the marketer’s observation of its product’s performance in the field.” George W. Conk, *The True Test: Alternative Safer Designs for Drugs and Medical Devices in a Patent-Constrained Market*, 49 UCLA L. REV. 737, 749 (2002). Lars Noah has argued in opposition to proposals like these that a “duty to investigate all foreseeable uses to which health care professionals might put an approved drug would be entirely unmanageable, and it would threaten to deprive intended users of a valuable product.” Noah, *supra* note 216, at 907.

220. See, e.g., PETER W. HUBER, *LIABILITY: THE LEGAL REVOLUTION AND ITS CONSEQUENCES* 155 (1988) (quoting statement of pharmaceutical company president that no one in his or her “right mind” would develop products for pregnant women because of the liability exposure); Fisk & Atun, *supra* note 98, at 26 (ascribing the failure to “test (let alone develop) drugs in pregnancy” to “risk aversion to the possibility of teratogenicity” which “is exacerbated by high lifelong settlement costs for a baby damaged in utero” and “by a jury-determined tort process, which favours punitive damages”); Vanessa Merton, *Impact of Current Federal Regulations on the Inclusion of Female Subjects in Clinical Studies*, in 2 WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES 65, 76 n.2 (Anna C. Mastroianni et al. eds., 1994) (predicting that, absent regulatory compulsion, liability concerns would remain “formidable obstacles to the participation of women as subjects in biomedical research”); Comment of DV Jr. to Ed Silverman, *Nothing in the Oven for Pregnancy Complications*, PHARMALOT, June 4, 2008, <http://www.pharmalot.com/2008/06/nothing-in-the-oven-for-pregnancy-complications> (“While acknowledging the problem, I have to say a drug company would be C-R-A-Z-Y to investigate a product in pregnant women in today’s litigation-friendly environment.”); Comment of Ol Cranky to Ed Silverman, *Nothing in the Oven for Pregnancy Complications*, PHARMALOT, June 4, 2008, <http://www.pharmalot.com/2008/06/nothing-in-the-oven-for-pregnancy-complications> (“The risk would have been way too huge for most companies to consider years ago – now it would be absolute suicide.”).

221. Randi Zlotnik Shaul et al., *Legal Liabilities in Research: Early Lessons from North America*,

the way the research was conducted caused harm, trial participants may have a negligence claim against the research sponsor to the extent that the sponsor failed to fulfill its duties to ensure that the investigators were well-qualified and to closely monitor their work.²²² Where it was the research intervention itself that caused the harm, plaintiffs have sued research sponsors on a variety of theories.²²³ Battery claims may be brought by research participants who allege that they did not know or did not consent to the research; negligence claims may be brought by participants who knew about the research and consented to participate in it, but who allege that they were not told everything they needed to know to make an informed decision.²²⁴ While a plaintiff participant's informed consent generally protects defendants from such allegations, when the participant is a pregnant woman and the injury is to her child, there is an added wrinkle because a fetus, of course, cannot give consent. That said, a child whose mother consented to participate in a clinical trial while pregnant probably could not successfully argue that he or she would not have given his or her consent.²²⁵

Although research-related litigation is more common than it once was, clinical trial participants, pregnant or not, bring relatively few liability claims and the body of case law remains small.²²⁶ Only four cases involving fetal harm brought on by participation in clinical trials have led to reported decisions.²²⁷ In all four, the plaintiffs claimed that

BMC MED. ETHICS 6:4, June 2005 <http://www.biomedcentral.com/content/pdf/1472-6939-6-4.pdf>.

222. 21 C.F.R. § 312.50 (2010).

223. See, e.g., *Craft v. Vanderbilt Univ.*, 18 F.Supp.2d 786, 789 (M.D. Tenn. 1998) (Plaintiffs, previously pregnant women and the children they were carrying, who were non-consenting subjects of experiments involving radioactive iron, sued under multiple federal and state law theories including battery, negligence, and medical malpractice.).

224. For example, in *Berman v. The Fred Hutchinson Cancer Research Ctr.*, No. C01-0727L (W.D. Wa. Aug. 8, 2002), the court found that the plaintiff's consent was invalid because she was promised, falsely, that she could receive a chemotherapy drug intravenously if she could not tolerate oral administration. Courts have also found that the failure to disclose certain conflicts of interest can invalidate consent. See, e.g., *Darke v. Estate of Isner*, 17 Mass. L. Rptr. 689 (Mass. Super. Ct. 2004) (holding that a doctor could be subject to medical malpractice liability under Massachusetts law for failing to disclose to his patient that he had a financial interest in the clinical trial that he recommended to his patient).

225. Anna C. Mastroianni, *HIV, Women, and Access to Clinical Trials: Tort Liability and Lessons from DES*, 5 DUKE J. GENDER L. & POL'Y 167, 179–80 (1998).

226. See Noah, *supra* note 216, at 839 n.293; Jill Wadlund, *Heading off a Clinical Trial Liability Lawsuit*, 12 APPLIED CLINICAL TRIALS 50, 50 (2003).

227. An unreported case of note is *Crayton v. UT Med. Group Inc.*, No. CT-007219-04 (Tenn. Cir. Ct. Dec. 28, 2004), which involved a pregnant woman who participated in a clinical trial evaluating the safety and efficacy of two drugs used to prevent maternal–fetal transmission of the HIV virus. Andrew M. Ballard, *Wrongful Death Lawsuit Filed in Tennessee Over Clinical Trial Using AIDS Drug Nevirapine*, MED. RES. L. & POL'Y REP., Jan. 2005, available at <http://healthcenter.bna.com/pic2/hc.nsf/id/BNAP-68LRCB?OpenDocument> (reporting on *Crayton*).

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they did not give their informed consent and in fact did not know that they were part of an experiment.²²⁸ These cases therefore provide only limited guidance on the extent of liability for fetal harm when a pregnant woman has consented to participate. It is clear from non-research-related case law that a pregnant woman can consent to medical treatment for herself and for her fetus.²²⁹ The informed consent provisions of the regulations governing the inclusion of pregnant women in clinical trials, which provide that consent can be given on behalf of a fetus by expectant mothers and fathers, support the conclusion that consent is as protective in the research context.²³⁰ Notably, case law authorizes parents to consent to their born children's participation in "therapeutic research that represents a valid alternative and may be the functional equivalent of treatment[.]"²³¹ While at least one court has limited parents' authority to consent to their children's participation in non-therapeutic research that poses more than a minimal risk,²³² the federal

The woman's baby was delivered by cesarean section after the woman developed severe side effects. *Id.* The woman died two days later. *Id.* The plaintiffs' claimed that the two defendant pharmaceutical companies "failed to adequately warn consumers of the potential adverse side effects associated with their products and were negligent in the design, manufacture, testing, advertising, warning, marketing, and sale of the drugs." *Id.*

228. See *Diaz v. Hillsborough County Hosp. Auth.*, No. 8:90-CV-120-T-25B, 2000 U.S. Dist. LEXIS 14061 (M.D. Fla. Aug. 7, 2000); *Craft*, 18 F. Supp. 2d 786; *Wetherill v. Univ. of Chicago*, 570 F. Supp. 1124 (N.D. Ill. 1983); *Mink v. Univ. of Chicago*, 460 F. Supp. 713 (N.D. Ill. 1978). The lead plaintiff in the *Diaz* case, Flora Diaz, participated in a study of drugs used to accelerate fetal lung development which randomized pregnant women between standard treatment with corticosteroids and an experimental combination of corticosteroids and thyroid hormone. Richard S. Saver, *Medical Research and Intangible Harm*, 74 U. CIN. L. REV. 941, 977 (2006). Her allegations with regard to the consent process have implications for research involving pregnant women generally. *Id.* Her counsel argued that she suffered from the therapeutic misconception, in part because of class and language barriers, but also because when her consent was sought she was experiencing a high-risk pregnancy and had been treated with pain-killing medications. *Id.* *Diaz* is noteworthy because it "was likely the first time research subjects recovered substantial monetary awards in the absence of credible physical injury claims." *Id.* at 978. After extensive discovery, the plaintiffs in *Diaz*, a certified class of approximately 5,000 pregnant women, settled with the defendant medical center for \$3.8 million. *Id.* The plaintiffs' novel dignitary harm constitutional claim was central to their success. *Id.* Ordinary informed consent and negligence claims would have failed because the plaintiffs and their babies did not receive standard medical care and could not demonstrate any physical harm. *Id.*

229. See *Miller v. Dacus*, 231 S.W.3d 903, 909–10 (Tenn. 2007) (citing cases).

230. 45 C.F.R. § 46.204(d), (e) (2010). Anna Mastroianni points to the Supreme Court's decision in *UAW v. Johnson Controls, Inc.* as further support for the claim "that the informed consent of the woman will preclude the imposition of liability," noting that the Court commented in dicta that "[i]f, under general tort principles, Title VII bans sex-specific fetal-protection policies, the employer fully informs the woman of the risk, and the employer has not acted negligently, the basis for holding an employer liable seems remote at best." Mastroianni, *supra* note 225, at 180 (quoting *UAW v. Johnson Controls, Inc.*, 499 U.S. 187, 208 (1991)).

231. *T.D. v. N.Y. State Office of Mental Health*, 650 N.Y.S.2d 173, 191–92 (N.Y. App. Div. 1996).

232. See *Grimes v. Kennedy Krieger Inst.*, 782 A.2d 807 (Md. 2001).

regulations governing research in pregnant women similarly do not allow non-therapeutic research that poses more than a minimal risk to fetuses.²³³

One cannot necessarily conclude from the limited number of lawsuits that clinical trial sponsors' potential exposure to liability is limited. Part or all of the explanation for the dearth of litigation is surely the dearth of research and development activity. Still, the limited number of participants in a clinical trial imposes a limit on the trial sponsors' exposure, and research injuries are not likely to be a significant source of liability. Even if research does not itself cause or risk causing physical harm, however, if it is conducted after a drug has been approved and is being marketed, it creates litigation risk. Should epidemiological or other research reveal a correlation between ingesting a company's drug while pregnant and maternal or fetal harm, some of the women who ingested the drug and were harmed are likely to sue, perhaps claiming, as the plaintiff in *Kilker* did, that the company knew of the risk before it conducted the research and failed to provide adequate warnings.²³⁴ GSK, the defendant in *Kilker*, defended itself at trial by arguing that when two epidemiological studies showed an association between Paxil and an increased risk of birth defects, GSK added the new information to the Paxil label as soon as it could.²³⁵ Today, GSK continues to maintain that Paxil does not, in fact, cause birth defects. Neither the company's faith in Paxil's safety, nor its timely inclusion of the study results on the Paxil label, was enough for it to win at trial, although either or both may explain the jury's decision not to award punitive damages.²³⁶

Many observers believe that research studying the effects of drugs on pregnant women and fetuses is especially susceptible to a liability barrier. In all pregnancies there is a background risk of an adverse outcome, irrespective of whether the mother took medication.

233. 45 C.F.R. § 46.204(b) (2010).

234. Noah, *supra* note 34, at 451 ("Courts sometimes struggle to determine precisely when a seller should have known that its product presented a risk of injury, whether the failure to provide a warning caused the plaintiff's injury given the fact that physicians may learn of new risk information from a variety of other sources, and whether the content and method selected for communicating the information was adequate in light of limitations in the way health care professionals discover and assimilate new information.").

235. Transcript of Closing Statement of Chilton Varner at 117, 127, 145, *Kilker v. SmithKline Beecham Corp.* (Pa. Ct. Com. Pl. Oct. 8, 2009) (No. 1813).

236. Kushner, *supra* note 193, at 541–42 ("[E]ven in the absence of data demonstrating an unsafe product, pharmaceutical manufacturers are not shielded from products liability or products liability litigation. Such suits disincentivize pharmaceutical manufacturers from postmarket safety testing because evidence of safety has little economic value if it does not reduce the costs of litigation and liability.").

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Approximately 17% of recognized pregnancies end in a miscarriage, which is defined for purposes of data collection as fetal death prior to twenty weeks gestation.²³⁷ Stillbirth, which is defined as fetal death after twenty weeks gestation, occurs in one in one hundred sixty deliveries.²³⁸ An estimated 3% of babies are born with major genetic or structural birth defects.²³⁹ Most miscarriages, stillbirths, and birth defects occur due to unknown causes. Environmental factors, defined to include drugs but also, among other things, infectious agents, cause approximately 10% of birth defects.²⁴⁰ Another 20% are genetic in origin.²⁴¹ Between 65% and 75% of birth defects are idiopathic, which means that they have no known cause.²⁴² Some percentage of the women whose children suffer from birth defects will blame medication they took during pregnancy for their children's injuries and will pursue litigation.²⁴³

Pregnancy and birth is considered a special case for a second reason: the potential for large damage awards due to the devastating nature of birth defects. A baby born with a birth defect may have expensive special needs for a long lifetime.²⁴⁴ Damage awards may also be high because innocent, injured babies are sympathetic plaintiffs.

Finally, pregnancy and birth is considered a special case because of the "long tail" of associated litigation. In every state a child who is born

237. Ventura et al., *supra* note 59, at 3, 24. The miscarriage rate for unrecognized pregnancies, that is, those that begin and end so early in gestation that the woman never knew she was pregnant, is believed to be much higher. *Id.* at 24.

238. Press Release, The American College of Obstetricians and Gynecologists, ACOG Issues New Guidelines on Managing Stillbirths (Feb. 20, 2009), http://www.acog.org/from_home/publications/press_releases/nr02-20-09-2.cfm.

239. Dept. of Health & Human Servs., Ctrs. for Disease Control & Prevention, *Update on Overall Prevalence of Major Birth Defects – Atlanta, Georgia, 1978–2005*, 57 MORBIDITY AND MORTALITY WEEKLY REP. 1, 2–3 (2008), available at <http://www.cdc.gov/mmwr/PDF/wk/mm5701.pdf>. See also C. Irl et al., *The PEGASUS Project* – A Prospective Cohort Study for the Investigation of Drug Use in Pregnancy*, 35 INT'L J. CLIN. PHARMACOLOGY & THERAPEUTICS 572, 572 (1997) ("The prevalence of congenital malformations requiring medical intervention or affecting the quality of life is about 70 per 1,000 births [i.e. 0.7%]. Accounting for approximately one third of all deaths in the first year of life, they represent the single most frequent cause of infant mortality . . ." (citations omitted)).

240. Irl et al., *supra* note 239, at 572.

241. *Id.*

242. *Id.*

243. Arthur Allen, *Prepare for a Vaccine Controversy*, N.Y. TIMES, Aug. 1, 2009, at WK10 ("[P]regnant women will be urged to get the vaccine because doctors have seen how H1N1 can cause especially nasty infections during pregnancy. But about one in seven pregnancies ends in a miscarriage, so nearly 1,500 of 10,000 women in early pregnancy will miscarry this fall—whether or not they get the H1N1 vaccine."); Elyse Tanouye, *Suits Involving Defunct Bendectin Chill Development of Pregnancy Medications*, WALL ST. J., June 22, 1993, at B1 ("[This] is a particularly daunting research area for the pharmaceutical companies because drugs can both cause birth defects and be blamed for ones that would have occurred anyway.").

244. Clayton, *supra* note 200, at 104.

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alive can assert a claim for harm done prenatally.²⁴⁵ In most states, these claims are tolled until the child reaches the age of majority.²⁴⁶ As an executive at PhRMA, the trade organization representing most pharmaceutical and biotechnology companies, told the *Wall Street Journal*, drug companies' research decisions are affected by the prospect of seemingly unending litigation exposure.²⁴⁷

There are reasons to question whether any or all of these factors make liability exposure for research studying the effects of drugs on pregnant women and fetuses uniquely large, unpredictable, or otherwise problematic. First, adverse events occur across therapeutic areas. There is a background risk of disability and death in all populations. Second, the potential for large damages awards and the long tail of loss obtain in whole or in part when drugs are developed to treat children. A legislative carrot-and-stick scheme has effectively incentivized pediatric drug development; the resultant products liability litigation has not been of note. Finally, off-label use of medication by pregnant women is widespread. Litigation has arisen where women and babies have experienced adverse events, but manufacturers have not been driven into bankruptcy due to the resultant damage awards.

In the absence of empirical data, it is impossible to know precisely how manufacturers perceive and weigh the tort system's competing incentives in the context of maternal–fetal medication research. What is clear is that exposure to liability is far from the only driver of company decision-making. Even if companies' exposure to liability is, on balance, a barrier to research, it would not follow that companies are “ready, willing, and able to conduct socially beneficial research, *but for* the costs of liability litigation and awards.”²⁴⁸

IV. PUBLIC POLICY APPROACHES TO CLOSING THE INFORMATION GAP

A. *Relief from Liability for Research*

In the pregnancy context and in other contexts where liability concerns are thought to be particularly salient, there are calls for relieving companies of the unpredictability of tort liability and compensating victims in an alternate system.²⁴⁹

245. *Id.*

246. *Id.* at 104 n.4.

247. Tanouye, *supra* note 243, at B1.

248. Wendy K. Mariner, *Compensation for Research Injuries*, in 2 WOMEN AND HEALTH RESEARCH: ETHICAL AND LEGAL ISSUES OF INCLUDING WOMEN IN CLINICAL STUDIES, 113, 118 (Anna C. Mastroianni et al. eds., 1994).

249. *See, e.g.*, Editorial, *Drug Development for Maternal Health Cannot Be Left to the Whims of*

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The highest profile example of such a system is the National Vaccine Injury Compensation Program (VICP).²⁵⁰ In the early 1980s, vaccine manufacturers' liability exposure was high, and they had difficulty securing liability insurance.²⁵¹ Concerns were raised about the exit of manufacturers from childhood vaccine production; by the end of 1984, only one manufacturer of the pertussis vaccine remained.²⁵² In 1986, after several attempts, Congress passed the National Vaccine Injury Compensation Act establishing the VICP.²⁵³ The twin goals of the VICP are (1) to offer the families of children injured by vaccines a no-fault alternative to the tort system that provides prompt and fair compensation and (2) to protect vaccine manufacturers from the specter of crippling liability which was threatening the vaccine supply.²⁵⁴ Claimants may be compensated for their medical expenses, loss of earning capacity, and reasonable attorney's fees and costs.²⁵⁵ Awards for pain and suffering are capped at \$250,000, and punitive damages are prohibited.²⁵⁶ If a vaccine causes death, the maximum award to the estate is \$250,000 plus reasonable attorney's fees and costs.²⁵⁷ The program is funded by an excise paid by patients of \$0.75 per dose;²⁵⁸ in

the Market, 5 PLOS MED. 841, 842 (2008) (arguing that any mechanism to encourage "the testing and collection of data on old and new drugs" in pregnancy would need to "specifically accept liability when harm occurs"); Lyerly et al., *supra* note 14 at 17 (recommending that "the liability concerns that animate so much of the behavior around research and drug development during pregnancy" be addressed at the federal and state levels); *see also, e.g.*, James M. Wood et al., *Product Liability for Stem Cell Research and Therapies – A Proposal*, 18 HEALTH LAWYER 1 (2005) (recommending adoption of an alternative compensation system for stem cell research); William M. Brown, *Déjà Vu All Over Again: The Exodus from Contraceptive Research and How to Reverse It*, 40 BRANDEIS L.J. 1 (2001) (contraceptive research); Andrew R. Klein, *A Legislative Alternative to "No Cause" Liability in Blood Products Litigation*, 12 YALE J. ON REG. 107 (1995) (blood products); Gregory C. Jackson, Comment, *Pharmaceutical Product Liability May Be Hazardous to Your Health: A No-Fault Alternative to Concurrent Regulation*, 42 AM. U. L. REV. 199 (1992) (all drug products); H. William Smith, III, Note, *Vaccinating AIDS Vaccine Manufacturers Against Product Liability*, 42 CASE W. RES. L. REV. 207 (1992) (AIDS vaccine).

250. National Childhood Vaccine Injury Act of 1986, 42 U.S.C. § 300aa-34 (2006).

251. Breslow, *supra* note 194, at 142 n.78 (quoting Wyeth Laboratories executive who testified before Congress that his company had stopped marketing the diphtheria, tetanus, and pertussis vaccine "because of extreme liability exposure, cost of litigation and the difficulty of continuing to obtain adequate insurance").

252. Notably, before the legislation creating the VICP was enacted, a second manufacturer resumed manufacturing and distributing the vaccine. Lainie Rutkow et al., *Balancing Consumer and Industry Interests in Public Health: The National Vaccine Injury Compensation Program and Its Influence During the Last Two Decades*, 111 PENN. ST. L. REV. 681, 696 (2007).

253. *Id.* at 688–703.

254. *Id.* at 684.

255. 42 U.S.C. § 300aa-15(a), (e)(1)(A) (2006).

256. *Id.* § 300aa-15(a)(4), (d).

257. *Id.* § 300aa-15(a)(2).

258. *Id.* § 300aa-15(i)(2); 26 U.S.C. § 9510(b)(1) (2006); 26 U.S.C. § 4131(a), (b) (2006).

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Fiscal Year 2011 the average award was \$1,041,874 plus attorney's fees and costs.²⁵⁹

The first step in the VICP process is filing a petition with the United States Court of Federal Claims.²⁶⁰ The Claims Court then forwards the petition to a VICP special master for decision.²⁶¹ Claimants are entitled to a presumption of causation if they show that they were administered a vaccine listed on the VICP Vaccine Injury Table and sustained a listed injury within a specified time period.²⁶² The table includes, among others, all vaccines recommended for "routine administration to children" by the CDC.²⁶³ The government can only avoid compensating a claimant who suffers a "table injury" by showing that the vaccine did not in fact cause the injury.²⁶⁴ Claims for conditions not listed on the table are evaluated on a case-by-case basis; claimants bear the burden of establishing that their condition was caused or exacerbated by a covered vaccine.²⁶⁵ Claimants are not required to prove that the vaccine manufacturer or administrator was at fault to recover.²⁶⁶

The special master's decision can be appealed to the Claims Court.²⁶⁷ The decision of the Claims Court can be further appealed to the United States Court of Appeals for the Federal Circuit, followed by the United States Supreme Court.²⁶⁸ Alternatively, after the Claims Court issues its decision, the claimant can decline any compensation proffered and sue the vaccine's administrator or manufacturer directly.²⁶⁹ Once in court, the National Vaccine Injury Compensation Act protects vaccine manufacturers from liability for injuries that are "unavoidable even though the vaccine was properly prepared and was accompanied by proper directions and warnings."²⁷⁰ They are also protected from

259. Health Res. & Servs. Admin., U.S. Dep't of Health & Human Servs., Nat'l Vaccine Injury Comp. Program, Statistics Reports, http://www.hrsa.gov/vaccinecompensation/statistics_report.htm (last visited Nov. 9, 2010).

260. 42 U.S.C. § 300aa-11(a)(1) (2006).

261. *Id.*

262. Rutkow et al., *supra* note 252, at 686 ("For example, a person would be eligible for VICP compensation if he or she received a measles, mumps, and rubella (MMR) vaccination and experienced anaphylactic shock zero to four hours later.").

263. 42 U.S.C. § 300aa-14(e) (2006).

264. *Id.* § 300aa-11(c)(1); 42 U.S.C. § 300aa-13(a)(1) (2006).

265. *Id.* § 300aa-11(c)(1)(C)(ii).

266. Rutkow et al., *supra* note 252, at 684.

267. 42 U.S.C. § 300aa-12(e) (2006).

268. *Id.* § 300aa-12(f).

269. *Id.* § 300aa-21.

270. *Id.* § 300aa-22(b)(1). With certain exceptions

a vaccine shall be presumed to be accompanied by proper directions and warnings if the vaccine manufacturer shows that it complied in all material respects with all requirements

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liability for failing to warn the injured party directly.²⁷¹ Manufacturers who can show that they complied “with all requirements under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act applicable to the vaccine and related to the vaccine injury or death with respect to which the action was brought” benefit from a rebuttable presumption against the award of punitive damages.²⁷²

Childhood vaccines are particularly appropriate for an alternative no-fault compensation system which guarantees recovery to victims. It is in the interest of public health for all or almost all children to be vaccinated and as a result, inoculation is a condition of entry to daycare and school.²⁷³ Because population-wide vaccination leads to “herd immunity,” there are positive externalities to each family’s choice to vaccinate.²⁷⁴ Unfortunately, there is also a negative internality. Vaccination brings with it a small but significant risk of harm, including anaphylactic shock, seizures, and death in previously healthy children.²⁷⁵ Because the number of children vaccinated is so high, the small risk that a vaccine will cause injury translates into substantial and predictable population-wide harm. This, in turn, exposes the vaccine’s manufacturer to substantial and potentially crippling liability.

Research into maternal–fetal medication risk is distinguishable from mass inoculation in important ways. Even if companies were to adopt more robust research agendas, the numbers involved would be much lower than is the case with inoculation. There is little reason to believe that the resultant liability would be so crippling that an alternative no-fault compensation system would be justified.

In its 1994 report *Women and Health Research*, the IOM explained that it considered “[t]he question of whether there should be a special

under the Federal Food, Drug, and Cosmetic Act . . . and section 351 of the Public Health Service Act . . . (including regulations issued under such provisions) applicable to the vaccine and related to vaccine-related injury or death for which the civil action was brought[.]

Id. § 300aa-22(b)(2). In October 2010, the Supreme Court heard oral argument in a case in which the plaintiff has challenged the scope of the National Vaccine Injury Compensation Act’s preemption provisions. See Posting of Matthew Scarola to SCOTUSblog, <http://www.scotusblog.com/2010/10/argument-recap-court-considers-vaccine-design-defect-liability/> (Oct. 14, 2010, 11:08 AM).

271. 42 U.S.C. § 300aa-22(c) (2006).

272. *Id.* § 300aa-23(d)(2).

273. Ross D. Silverman, *Litigation, Regulation, and Education – Protecting the Public’s Health through Childhood Immunization*, 360 NEW ENG. J. MED. 2500, 2501 (2009).

274. Anthony Ciolli, *Religious & Philosophical Exemptions to Mandatory School Vaccinations: Who Should Bear the Costs?*, 74 MO. L. REV. 287, 297 (2009) (explaining that if a “relatively small percentage of a religious community’s population” decide against immunization, the negative externalities could include a loss of herd immunity and a resulting epidemic).

275. Rutkow et al., *supra* note 252, at 681.

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compensation scheme for injuries sustained by children as a result of a parent's participation in a clinical study."²⁷⁶ The IOM determined that a special compensation scheme that would cover children harmed prenatally by experimental drugs taken by their mothers during pregnancy would be impracticable because of "especially difficult problems with regard to establishing causation and averting large numbers of questionable recoveries."²⁷⁷ Establishing causation would be even more problematic if the special compensation scheme were to cover a company's exposure to liability from the lawsuits that would inevitably follow an announcement that maternal-fetal medication research sponsored by the company had identified a safety concern.

Most importantly, there is little reason to believe that adoption of an alternative system would induce manufacturers to implement robust maternal-fetal research agendas. Shortages of childhood and other vaccines persist. In late 2004, in the wake of an announcement from Chiron Corporation that it would not be able to provide flu vaccine for the United States market that year due to manufacturing-related safety concerns, Congress passed legislation adding the flu vaccine to the list of vaccines covered by the VICP.²⁷⁸ Interestingly, while members of Congress speculated that fear of litigation was driving flu vaccine manufacturers from the market, adding the flu vaccine to the VICP has not lead to an increase in manufacturer participation in the flu vaccine market. Michelle Mello and Troyen Brennan predicted as much in a 2005 article in *JAMA*, noting that the undersupply problem is complex and that "the historical record provides cause for skepticism that liability relief alone will prevent another flu vaccine shortage."²⁷⁹

B. Rewarding Research with an Extended Period of Exclusivity

Children and pregnant women are, or were, similarly situated in that both must contend with a dearth of information about drug efficacy and safety. Unlike pregnant women and fetuses, children have been the beneficiary of key legislation designed to end their status as "therapeutic orphans."²⁸⁰ In 1997, Congress enacted the pediatric exclusivity provision of the U.S. Food and Drug Administration Modernization Act (FDAMA), which authorized the FDA to extend a drug's period of

276. INST. OF MED., *supra* note 146, at 169.

277. *Id.*

278. Rutkow et al., *supra* note 252, at 726.

279. Michelle M. Mello & Troyen A. Brennan, *Legal Concerns and the Influenza Vaccine Shortage*, 294 *JAMA* 1817, 1820 (2005).

280. Cohen, *supra* note 124, at 662 (quoting S. REP. NO. 105-43, at 3 (1997)).

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exclusivity if the drug’s manufacturer agreed to conduct “pediatric studies,” defined as at least one clinical investigation in children.²⁸¹ In 2002, the pediatric exclusivity provision was reenacted as part of the Best Pharmaceuticals for Children Act (BPCA);²⁸² the BPCA was reauthorized in 2007 in Title V of the Food and Drug Administration Amendments Act (FDAAA).²⁸³

The pediatric exclusivity provision provides that when a drug is still under a patent or other exclusivity term, a company may be awarded an additional six months of exclusivity for the entire active moiety—that is, for all of the drug’s formulations and indications—in exchange for completing FDA-requested safety, efficacy, or pharmacokinetic pediatric studies.²⁸⁴ If the FDA “determines that information relating to the use of an approved drug in the pediatric population may produce health benefits in that population,” it may issue a formal request of the drug’s manufacturer, asking it to conduct the necessary study or studies.²⁸⁵ The manufacturer is free to decline the agency’s requests and is especially likely to do so if a drug is no longer in an exclusivity period, as there would be no incentive to conduct the research in that case.²⁸⁶

Once the study or studies are completed, the FDA decides if exclusivity is merited. Outcome is irrelevant. There is no requirement that the studies establish that the drug is safe and effective in children or even that they generate valuable information about pediatric use.²⁸⁷ Exclusivity is awarded if the studies fairly respond to the agency’s written request, are conducted in accordance with commonly accepted scientific principles and protocols, and are properly submitted.²⁸⁸ Whenever exclusivity is granted, the BPCA requires the FDA to review all adverse events occurring in children for the next year, as well as all of the adverse events that occurred in children in previous years; the results of the review are presented to the FDA’s Pediatric Advisory Committee, which advises the FDA on whether and how to respond.²⁸⁹ The FDA is also required to order a labeling change whenever an agency-requested pediatric study “does or does not demonstrate that the

281. *Id.* at 663–65.

282. *Id.* at 667.

283. Food and Drug Administration Amendments Act of 2007, Pub. L. No. 110-85, §§ 501–505A, 121 Stat. 823, 876–89 (to be codified at 21 U.S.C. § 355a).

284. 21 U.S.C.A. § 355a (West 2010).

285. *Id.* § 355a(c)(1).

286. Cohen, *supra* note 124, at 666.

287. Eisenberg, *supra* note 86, at 730.

288. 21 U.S.C.A. § 355a(b)(1), (c)(1) (West 2010).

289. *Id.* § 355a(l).

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drug that is the subject of the study is safe and effective, including whether such study results are inconclusive, in pediatric populations or subpopulations.”²⁹⁰ The BPCA does not empower the FDA to order manufacturers to produce and distribute age-appropriate formulations, even when medicines are found to be safe and effective for use in children.²⁹¹

If a manufacturer chooses not to conduct an FDA-requested study of an on-patent drug, the FDA may ask whether the Foundation for the National Institutes of Health (FNIH) has sufficient funding “to initiate and fund all of the studies in the written request in their entirety within the timeframes specified within the written request.”²⁹² If the FNIH has sufficient funding, the statute requires it to fund the studies. If it does not, the statute requires the FDA to “consider” whether to exercise its authority under the Pediatric Research Equity Act (PREA) to require that the company conduct the study.²⁹³

As of November 30, 2009, the FDA had issued 377 written requests for pediatric studies of drugs prescribed to children, 306 of which were issued following a proposal from the manufacturer.²⁹⁴ By early 2007, “the program ha[d] generated more than 300 pediatric studies[,]”²⁹⁵ and “nearly half of the 10 drugs most frequently prescribed for children” had “been studied under the BPCA.”²⁹⁶ While there were only eleven pediatric labeling changes between 1990 and 1997, there were one hundred thirty between 1997 and 2007.²⁹⁷ According to a chart posted on the FDA’s website, pediatric studies conducted in response to the agency’s requests had resulted in 184 labeling changes by the end of 2009.²⁹⁸ However, the authors of a 2007 *JAMA* article estimated that only a “third of the labeling changes [since the start of the program] showed an important difference in the pediatric dosing, safety, or

290. *Id.* § 355a(j).

291. *Id.* § 355a(e)(2), (f)(6)(D).

292. *Id.* § 355a(n)(1)(A).

293. *Id.*

294. U.S. Food & Drug Admin., Pediatric Exclusivity Statistics as of November 30, 2009, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050006.htm> (last visited Jan. 7, 2010).

295. Jennifer S. Li et al., *Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program*, 297 *JAMA* 480, 480 (2007).

296. U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-07-557, PEDIATRIC DRUG RESEARCH: STUDIES CONDUCTED UNDER BEST PHARMACEUTICALS FOR CHILDREN ACT 5 (2007).

297. Carissa M. Baker-Smith et al., *The Economic Returns of Pediatric Clinical Trials of Antihypertensive Drugs*, 156 *AM. HEART J.* 682, 682 (2008).

298. U.S. FOOD & DRUG ADMIN., PEDIATRIC LABELING CHANGES THROUGH DECEMBER 24, 2009 (2009), <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf>.

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efficacy compared with adult patients.”²⁹⁹ Even more concerning, a subsequent study revealed that information on less than half of the products found to have safety concerns when used by children was published in the peer-reviewed literature and that close to half of the articles that were published did not accurately reflect the FDA’s review.³⁰⁰

The pediatric exclusivity provision is off-budget, and it is popular with the innovator drug industry.³⁰¹ It is unsurprising that Congress has reauthorized it three times. Questions have arisen about how effective it has been at solving the information problem. Some of the drugs studied are rarely prescribed to children, while important drugs that are off-patent and no longer subject to exclusivity have gone unexamined.³⁰² Because companies have no incentive to conduct follow-up research, questions such as why a drug had a higher adverse event rate in children remain unanswered, and although many pressing questions about medication use in children can only be answered with epidemiological research, such studies do not “count” toward exclusivity. Companies also have an incentive to wait until their drugs are nearing the end of their patent life to pursue the BPCA’s additional six months of exclusivity. This is only partially remedied by FDAAA’s requirement that companies must complete the process at least nine months prior to the expiration of the existing patent or exclusivity period in order to qualify for the extension.³⁰³

In addition, many critics of the pediatric exclusivity provision complain that the benefit to companies of six months of exclusivity dwarfs the cost of conducting the requisite clinical trials. A 2007 study evaluated nine drugs, each from a different therapeutic area, for which pediatric data were submitted from 2002 to 2004.³⁰⁴ Median cash inflows were \$140 million, while median cash outflows were just \$10 million.³⁰⁵ The median net economic benefit accruing to the drugs’

299. Li et al., *supra* note 295, at 487. The GAO is more generous, determining that 87 percent of the drugs granted pediatric exclusivity between 2002 and 2005 had “important labeling changes” as a result of the studies conducted. U.S. GOV’T ACCOUNTABILITY OFFICE, *supra* note 296, at 4.

300. Daniel K. Benjamin, *Safety and Transparency of Pediatric Drug Trials*, 163 ARCHIVES PEDIATRICS & ADOLESCENT MED. 1080, 1083 (2009).

301. See *Programs Affecting Safety and Innovation in Pediatric Therapies: Hearing Before the Subcomm. on Health of the H. Comm. on Energy and Commerce*, 110th Cong. (2007) (Statement of Lori M. Reilly, Vice President, Policy & Research, Pharmaceutical Research Manufacturers of America), <http://energycommerce.house.gov/images/stories/Documents/Hearings/PDF/110-he-hrg.052207.Reilly-testimony.pdf> (urging reauthorization of both the BPCA and the PREA).

302. Noah, *supra* note 28, at 282–83.

303. 21 U.S.C.A. § 355a(b)(2), (c)(2) (West 2010).

304. Li et al., *supra* note 295, at 481.

305. *Id.* at 483–84. A 2006 industry survey yielded a higher estimated cost: \$20 million to

manufacturers was \$132 million, with a range from -\$8.9 million to \$507 million. The authors cautioned that five of the nine drugs studied were blockbusters, meaning that they had more than \$1 billion in sales. For products with lower sales, the inflow would be lower.³⁰⁶

A more recent study found that the median cost to evaluate one of nine hypertension drugs for which completed pediatric study reports were submitted to the FDA between 1997 and 2004 was \$6 million, with the median cost of clinical trials (\$4.3 million) far exceeding that of bioequivalence or bioavailability studies (\$731,856) and pharmacokinetic studies (\$1.1 million).³⁰⁷ The after-tax, inflation-adjusted median cash outflow to pay for FDA-requested studies was \$4.8 million, while the median cash inflow over the six month exclusivity period was \$60 million.³⁰⁸ There was a wide range in net return-to-investment, although in all cases the net return was positive. Just under half of the drugs studied had a return on the dollar of less than \$10, while just over half had a return of greater than \$20.³⁰⁹

In addition to generating windfall profits for pharmaceutical companies, the additional six months of exclusivity costs consumers, especially the elderly, hundreds of millions of dollars by delaying the launch of cheaper, generic drugs.³¹⁰ It also increases costs borne by health care payors, including the government, which with the advent of Medicare Part D is paying a larger portion of the country's medication costs than ever before.³¹¹ One commenter has argued that it would be less expensive and more efficient if pharmaceutical companies declined to perform any pediatric studies in response to the FDA's requests and the government conducted them instead.³¹² The host of concerns about the pediatric exclusivity provision's cost and efficiency make it difficult to conclude that it should be expanded to include pregnant women and fetuses.

complete a BPCA written request. Christopher-Paul Milne & Jon B. Bruss, *The Economics of Pediatric Formulation Development for Off-Patent Drugs*, 30 *CLINICAL THERAPEUTICS* 2133, 2138 (2008). Milne and Bruss point out that the estimates used by Li and his co-authors do not include the cost of developing pediatric formulations of a drug. *Id.* They note that multiple formulations may be necessary to meet the needs of children at various stages of development; they could include "suspensions, sprinkles, oral solutions, coated granules for reconstitution in water, and adult pumps converted to deliver smaller doses." *Id.*

306. Li et al., *supra* note 295, at 484–85.

307. Baker-Smith et al., *supra* note 297, at 685.

308. *Id.*

309. *Id.* at 686.

310. Breslow, *supra* note 194, at 167–69.

311. See THE HENRY J. KAISER FAMILY FOUND., *PRESCRIPTION DRUG TRENDS* (2010), available at <http://www.kff.org/rxdrugs/upload/3057-08.pdf>.

312. Breslow, *supra* note 194, at 189.

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The reauthorized BPCA requires that the NIH, in consultation with the FDA and outside experts, publish a list of the highest priority diseases or conditions in which medication–related knowledge gaps negatively affect the children who suffer from them.³¹³ Funds are to be awarded

to entities that have the expertise to conduct pediatric clinical trials or other research (including qualified universities, hospitals, laboratories, contract research organizations, practice groups, federally funded programs such as pediatric pharmacology research units, other public or private institutions, or individuals) to enable the entities to conduct the drug studies or other research on the issues

on the list.³¹⁴ Drugs that are off-patent that the FDA determines should be studied in children are among those to be included on the list.³¹⁵

This is a sensible approach to closing the information gap—albeit one which critics charge has “never been appropriately funded”—and it should be extended to include pregnant women for a number of reasons, the first being that the government can conduct research more cheaply than it can incentivize research.³¹⁶ Also, unlike children, pregnant women do not typically need drugs to be formulated specifically for them. Reformulation is one of the central challenges of pediatric research and one in which the involvement of the manufacturer is key.³¹⁷ In addition, when the government funds research, it does not need to factor in whether drugs are on- or off-patent or in an exclusivity period; it does not even need to constrain itself to studies of a single drug.³¹⁸ In the maternal–fetal research arena, the government would be free to consider whether, instead of a drug by drug effort, it would be preferable to perform basic research into pregnancy’s pharmacokinetic and pharmacodynamic effects or into the mechanisms of human

313. 42 U.S.C.A. § 284m (West 2010).

314. *Id.* § 284m(b).

315. 21 U.S.C.A. § 355a(n)(1)(B) (West 2010).

316. Benjamin, *supra* note 300, at 1085. *Cf.* Roin, *supra* note 89, at 561 (noting the government’s “history of grossly underfunding clinical research”).

317. Milne & Bruss, *supra* note 305, at 2138–39 (“[M]anufacturers who attempt to respond to Written Requests must begin the investigation with a highly resource-intensive, time-consuming, and risky experiment in formulation development.”).

318. Another way to address this would be to de-link the grant of market exclusivity from a drug’s patent term, that is, to grant exclusivity to any manufacturer who studied any drug, whether on- or off-patent, in pregnant women. *See* Roin, *supra* note 89, at 564 (recommending that Congress authorize the FDA to reward companies that submit new drug applications for drugs with weak or no patent protection with periods of exclusivity).

teratogenicity.³¹⁹

Finally, research conducted with government or other noncommercial support has or should have the advantage of relative trustworthiness.³²⁰ Pharmaceutical manufacturers must engage in a constant painstaking weighing of their duties to shareholders, their common law duties, and their regulatory obligations. Manufacturers know that if research they sponsor associates their product with an increased risk of harm, they could suffer a laundry list of negative sequelae, ranging from being asked to conduct additional testing or implement marketing restrictions, to a reduction in sales, to the withdrawal of their product from the market altogether. Sidestepping the potential conflict between a manufacturer's roles as profit-making public company and research sponsor is an additional benefit of government-funded research.³²¹

Significant strides have already been made as a result of government-funded research. For example, in 2006, grants from the Agency for Healthcare Research and Quality and from the FDA supported epidemiological research that revealed that a class of high blood pressure drugs doctors had long believed to be safe for use in early pregnancy in fact increased the rate of birth defects.³²² More recently,

319. Cf. Mitchell, *supra* note 14, at 2557 ("It is a matter of concern that pregnancy registries for specific drugs, often operated by manufacturers, seek to recruit patients receiving different drugs into separate registries and a patient receiving multiple drugs into multiple registries. Such competition for patients and practitioners can and may dilute or fragment the efforts of pregnancy registries that focus on a wide range of drugs.").

320. Kevin Outterson, *Death from the Public Domain?*, 87 TEX. L. REV. SEE ALSO 45, 53 (2009), <http://www.texasrev.com/sites/default/files/seealso/vol87/pdf/87TexasLRevSeeAlso45.pdf> (suggesting that the benefit of avoiding bias could compensate in whole or in part for any inefficiencies associated with government funding).

321. This is not to suggest that government-funded research is always free of conflicts of interest. Notably, investigators who receive government funding to conduct clinical research often have financial relationships with pharmaceutical companies as well. See, e.g., Letter from Charles E. Grassley, Ranking Member, U.S. Senate Comm. on Fin., to James W. Wagner, President, Emory Univ. (June 2, 2009), http://s.wsj.net/public/resources/documents/WSJ_LtrEmoryUni_090609.pdf (discussing the case of Dr. Zachary Stowe, who in 2007 received \$154,400 from GlaxoSmithKline, much of it for talks promoting GSK's antidepressants, at the same time that he served as principal investigator on several NIH grants related to antidepressant use by pregnant women). The NIH has announced plans to amend its conflict of interest regulations to better police these relationships. Responsibility of Applicants for Promoting Objectivity in Research for Which Public Health Service Funding Is Sought and Responsible Prospective Contractors; Proposed Rule, 75 Fed. Reg. 28,688, 28,689 (May 21, 2010).

322. William O. Cooper et al., *Major Congenital Malformations after First-Trimester Exposure to ACE Inhibitors*, 354 NEW ENG. J. MED. 2443, 2448 (2006). In an accompanying editorial, J.M. Friedman opined as follows:

Clearly, more research on the teratogenic potential of ACE inhibitors in early pregnancy is needed. This is not the last word on the subject, but it is shocking to realize that it is almost the first.

....

Not knowing the teratogenic risks of these drugs really does matter. . . . Birth defects

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the CDC-funded National Birth Defects Prevention Study, a multi-site epidemiological study of women whose pregnancies were affected by major birth defects, yielded valuable information about two classes of antibiotics used to treat urinary tract infections, namely that they are associated with an increased risk of several birth defects when used in early pregnancy.³²³

In an effort to close the information gap, a group of physicians and ethicists from Duke University, Georgetown University, and Johns Hopkins University recently started a project called “The Second Wave: Toward the Responsible Inclusion of Pregnant Women in Research.”³²⁴ While the decision to direct government funds to research benefiting a particular population or disease, as opposed to funding research benefiting another population or disease or to funding treatment, involves a complex weighing of bioethical and social justice concerns,³²⁵ members of the Second Wave contend that stepping up research efforts in pregnant women is just because they “have long been underrepresented in research” and “they and their needs have been substantially absent from social investments to advance medical knowledge.”³²⁶ In the summer of 2009, Second Wave advocates successfully lobbied to have language inserted into the house committee report accompanying the Departments of Labor, Health and Human Services and Education Fiscal 2010 Appropriations measure encouraging the NIH “to expand research on pregnant women with the goals of better understanding the long-term health effects on women of disease states in pregnancy, the proper therapeutics for pharmacologic treatments for pregnant women who face illness, and the safety and efficacy of medications administered to pregnant women and fetuses.”³²⁷

caused by teratogenic treatments are preventable, and babies and their mothers are being harmed unnecessarily because we do not know enough about which treatments to use and which to avoid.

J.M. Friedman, *ACE Inhibitors and Congenital Anomalies*, 354 *NEW ENG. J. MED.* 2498, 2499 (2006).

323. Krista S. Crider et al., *Antibacterial Medication Use During Pregnancy and Risk of Birth Defects*, 163 *ARCHIVES OF PEDIATRICS & ADOLESCENT MED.* 978, 978–79 (2009).

324. The Second Wave: Toward the Responsible Inclusion of Pregnant Women in Medical Research, <http://kennedyinstitute.georgetown.edu/secondwave/>; <http://www.bioethicsinstitute.org/WEB/PAGE/901/SECTIONID/379/PAGELEVEL/2/INTERIOR.ASP#> (last visited Feb. 23, 2010).

325. Rebecca Dresser, *Priority Setting in Biomedical Research*, 11 *VIRTUAL MENTOR* 322, 322–25 (2009), <http://virtualmentor.ama-assn.org/2009/04/msoc1-0904.html>.

326. Lyerly et al., *supra* note 17, at 3. The Second Wave organized a meeting of a group of experts including government officials in April 2009 “to identify barriers, articulate the costs of ignorance, and fashion consensus proposals that can immediately begin to make a difference in pregnant women’s health.” The Second Wave: Toward the Responsible Inclusion of Pregnant Women in Medical Research, <http://kennedyinstitute.georgetown.edu/secondwave/>, <http://www.bioethicsinstitute.org/WEB/PAGE/901/SECTIONID/379/PAGELEVEL/2/INTERIOR.ASP#> (last visited Feb. 23, 2010).

327. H.R. Rep. No. 111-220, at 136 (2009).

On December 30, 2009, the FDA announced the creation of the Medication Exposure in Pregnancy Risk Evaluation Program (MEPREP).³²⁸ Through MEPREP, the FDA will fund and conduct, in collaboration with private researchers, “research to study the effects of prescription medications used during pregnancy.”³²⁹ The participating sites, which include the HMO Research Network Center for Education and Research in Therapeutics (CERT), Kaiser Permanente’s multiple research centers, and Vanderbilt University, “have health care information for about 1 million births over the past seven years (2001–2007),” which the researchers will systematically retrieve and analyze.³³⁰ MEPREP will be led by a steering committee with representatives from the FDA and from each participating site.³³¹ In the press release announcing the program, Commissioner of Food and Drugs Margaret Hamburg is quoted as follows: “This program is a great example of FDA and the private sector working together to improve the health of pregnant women and their children. These data will guide regulatory policy and influence medical practice.”³³²

The FDA’s Sentinel System is another example of a public–private partnership with the potential to generate valuable information about maternal–fetal medication risk. Section 905 of FDAAA requires that the agency establish “a postmarket risk identification and analysis system to link and analyze safety data from multiple [public and private] sources.”³³³ The statute specifies that the agency’s eventual goal should be to include data on at least 100 million patients.³³⁴ Once established, the Sentinel System will allow the FDA “to actively monitor the safety of medical products continuously and in real-time.”³³⁵ With the establishment of the System, the FDA will also be well-positioned to implement the recommendation of Dr. Allen Mitchell of the Slone Epidemiology Center at Boston University that the agency bring coherence and organization to the current patchwork of pregnancy registries (in which pregnant women who are exposed to a medication

328. Press Release, U.S. Dept. of Health & Human Servs., Food & Drug Admin., Health Organizations to Study Safety of Medications Taken During Pregnancy (Dec. 30, 2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2009/ucm195934.htm>.

329. *Id.*

330. *Id.*

331. *Id.*

332. *Id.*

333. 21 U.S.C.A. § 355(k)(3)(B)(ii) (West 2010).

334. *Id.*

335. U.S. Food & Drug Admin., FDA’s Sentinel Initiative – Background, <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm149340.htm> (last visited May 3, 2010).

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are followed to determine associated outcomes)³³⁶ and case-control studies (in which women who give birth to babies born with birth defects are compared to a control group of women whose babies were born healthy).³³⁷ Finally, if the Sentinel System does not generate answers to “priority drug safety questions,” including “the safety of use in domestic populations not included, or underrepresented, in the trials used to approve the drug (such as . . . pregnant women . . .),” § 905 authorizes the FDA to contract with an outside entity to conduct a complementary investigation.³³⁸

Manufacturers should also be required to fund maternal–fetal medication research in appropriate cases.³³⁹ In the pediatric arena, the Pediatric Research Equity Act (PREA) requires that, as a condition of FDA approval of a new drug application or supplemental drug application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration, drugs be studied in children. Applicants must submit a “pediatric assessment” which evaluates the drug’s safety and effectiveness for use in children and “support[s] dosing and administration” for any pediatric sub-populations for which the drug is found to be safe and effective.³⁴⁰ The PREA also requires applicants to request approval of the formulations appropriate for those sub-populations for which the drug is found to be safe and effective.³⁴¹

A deferral provision addresses concerns about delaying drugs’ time to market.³⁴² In addition, the pediatric research requirement does not apply if the “course of the disease and the effects of the drug are sufficiently

336. Angela Scheuerle et al., *Measurements of Birth Defect Prevalence: Which Is Most Useful as a Comparator Group for Pharmaceutical Pregnancy Registries?*, 85 BIRTH DEFECTS RESEARCH PART A: CLINICAL AND MOLECULAR TERATOLOGY 611, 619 (2009) (“Pregnancy registries are designed to monitor for ‘signals’ of increased risk and to provide reassurance when sufficient unaffected exposed pregnancies are collected.”); Kristine E. Shields et al., *Monitoring Outcomes of Pregnancy Following Drug Exposure*, 27 DRUG SAFETY 353, 353 (2004) (“[T]he strength of the registry lies in its ability to gather pregnancy outcome reports early in the life of a product and to recognise and analyse unusual birth defects.”); Dianne L. Kennedy et al., *Pregnancy Exposure Registries*, 27 DRUG SAFETY 215, 218 (2004) (noting that registries are “seriously constrained” in their ability to detect modest increases in risk in the range of two to five-fold).

337. Mitchell, *supra* note 14, at 2558.

338. 21 U.S.C.A. § 355(k)(4)(D)(i)(II)(bb) (West 2010).

339. Human Rights Council, *Report of the Special Rapporteur on the Right of Everyone to the Enjoyment of the Highest Attainable Standard of Health, Paul Hunt, Annex, Mission to GlaxoSmithKline*, ¶ 40, U.N. Doc. A/HRC/11/12/Add.2 (May 5, 2009) (prepared by Paul Hunt) (“Pharmaceutical companies also have a responsibility to ensure that medicines are developed for . . . pregnant and lactating women . . .”).

340. 21 U.S.C.A. § 355c (a) (West 2010).

341. *Id.* § 355c (d).

342. *Id.* § 355c (a)(3).

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similar in adults and pediatric patients [such] that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies.”³⁴³ The FDA can also waive the pediatric research requirement, if (1) the “necessary studies are impossible or highly impracticable,” (2) there is evidence strongly suggesting that the drug would be ineffective or unsafe in children, or (3) the drug “does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients” and “is not likely to be used in a substantial number of pediatric patients.”³⁴⁴ A partial waiver can be granted on the same grounds and “on the ground that it is not possible to develop a pediatric formulation.”³⁴⁵

The PREA also empowers the FDA to require that a manufacturer study one of its already-approved drugs, if the manufacturer declines to study the drug voluntarily pursuant to the BPCA and the FNIH lacks funds to conduct the study, under the following circumstances: (1) the drug is taken by a substantial number of children for the labeled indications and adequate labeling could benefit pediatric patients; (2) there is reason to believe the drug would be a meaningful improvement over existing therapies for children for one of the labeled indications; or (3) the absence of adequate labeling could pose a risk to pediatric patients.³⁴⁶ As of December 24, 2009, the labels of 121 medications had been changed as a result of studies submitted pursuant to PREA.³⁴⁷

The PREA should be extended to benefit pregnant women and fetuses, as well as children. While the provision that manufacturers first be afforded the opportunity to conduct maternal–fetal research voluntarily in exchange for an additional period of exclusivity would not apply, the requirement that FDA seek funding from the FNIH before ordering a manufacturer to study an already-approved drug could. In addition, the same or similar exception and waiver provisions that are in place for the pediatric research requirements could be made available for maternal–fetal research. Also serving to mitigate any hardship to manufacturers would be the ability of the FDA to grant a deferral of the required research until after a new drug is approved for any “appropriate

343. *Id.* § 355c (a)(2)(b).

344. *Id.* § 355c (a)(4).

345. *Id.*

346. *Id.* § 355c(b).

347. U.S. FOOD & DRUG ADMIN., DEP’T OF HEALTH & HUMAN SERVS., PEDIATRIC LABELING CHANGES THROUGH DECEMBER 24, 2009 (2009), <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PediatricTherapeuticsResearch/UCM163159.pdf>.

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reason.”³⁴⁸ In its draft Guidance for Industry on complying with the PREA, the FDA:

recognizes that in certain cases scientific and ethical considerations will dictate that pediatric studies should not begin until approval of the drug or biological product for use by adults—for example, where a product has not shown any benefit over other adequately labeled products in the class, the therapeutic benefit is likely to be low, or the risks of exposing pediatric patients to the new product may not be justified until after the product’s safety profile is well established in adults after initial marketing.³⁴⁹

These considerations apply to maternal–fetal research as well.

Even if the PREA is not extended, the FDA can and should make full use of its power to require, where appropriate, the establishment of a pregnancy registry and a plan for pregnancy-related post-marketing surveillance as conditions of approval.³⁵⁰ In addition, FDAAA authorizes FDA to require post-marketing studies and clinical trials where necessary to: (1) assess a known serious risk of a drug; (2) assess signals of serious risk; and (3) identify unexpected serious risks where the data indicates the potential for such risks.³⁵¹ In a draft Guidance for Industry issued in July 2009, the FDA gave as an example of a post-marketing requirement under FDAAA a clinical trial designed to evaluate the safety of a drug in pregnant women.³⁵² Notably, FDAAA does not authorize the FDA to require companies to conduct clinical trials designed to study products’ efficacy. In the draft Guidance, the FDA notes that efficacy trials would be considered for agreed-upon post-market commitments, as opposed to agency-mandated requirements.³⁵³ Before FDAAA, the FDA entered into voluntary agreements with manufacturers to conduct post-market trials and studies, but companies routinely failed to follow through on their

348. 21 U.S.C.A. § 355c(a)(3) (West 2010).

349. OFFICE OF THE COMM’R, U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: HOW TO COMPLY WITH THE PEDIATRIC RESEARCH EQUITY ACT 9 (2005).

350. PETER BARTON HUTT ET AL., FOOD AND DRUG LAW 727 (3rd ed. 2007) (explaining that while the FD&C Act does not explicitly authorize the FDA to condition approval on a commitment to conduct postapproval testing, the agency has been doing so since the 1960s); Kennedy et al., *supra* note 336, at 218 (“When the purpose of the pregnancy exposure registry is to assess margins of safety of a product or to monitor for potential harm, it is appropriate to initiate the registry as soon as possible, such as at the time of initial marketing, when a new indication is approved, or when patterns of use reveal that the product is used by women of reproductive age.”).

351. 21 U.S.C.A. § 355(o)(3)(B) (West 2010).

352. OFFICE OF THE COMM’R, U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND CLINICAL TRIALS – IMPLEMENTATION OF SECTION 505(O) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 7 (2009).

353. *Id.* at 8.

commitments.³⁵⁴ FDAAA creates a standard process and timeframe for negotiating post-marketing requirements and agreed-upon commitments and authorizes the FDA to track companies' progress using a timetable for completion and periodic reports.³⁵⁵ FDAAA also provides for fines for non-compliance;³⁵⁶ previously, the FDA's formal enforcement arsenal was limited to the drastic remedy of withdrawal of approval.³⁵⁷

V. CONCLUSION

Real moral and scientific conundrums arise in maternal–fetal medicine. There will always be information that is out of reach because it can only be gleaned from clinical trials that are scientifically impossible, ethically inappropriate, or financially unjustifiable. The information gap is deeper and wider than that, however. Ruth Faden, director of the Berman Institute of Bioethics at Johns Hopkins University and a leader of the Second Wave movement, describes it this way: “Everyone thinks, Oh, my God, research on pregnant women! All kinds of ethical flags go up. We don't have to start with high drama. [There's enough] low-hanging fruit that we could keep lots of medical researchers busy for a long time.”³⁵⁸

Because maternal–fetal medication research is underproduced by the private market, government intervention is warranted. The most direct approach—government-funded research and government-mandated research—is likely to be the most effective and efficient. Eliminating the liability barrier facing pharmaceutical companies is unlikely to be effective, while offering an extended period of exclusivity as a “voluntary incentive” to private-sector research is grossly inefficient. Increased funding of public-private partnerships like MEDREP combined with increased responsibility on the part of drug companies to research their products, not just in children but in pregnant women and fetuses as well, are promising approaches to providing pregnant women with the data they need to reason well about the daunting questions they face when illness strikes.

354. See, e.g., Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies; Availability, 72 Fed. Reg. 5069, 5070 (Feb. 2, 2007) (reporting that 37% of new drug applications and abbreviated new drug applications and 47% of biologics license applications had “open postmarketing commitments with annual reports due, but not submitted within 60 days of the anniversary date of U.S. approval.”).

355. 21 U.S.C.A. § 355(o)(3)(E) (West 2010).

356. *Id.* § 333(f)(4)(A).

357. HUTT ET AL., *supra* note 350, at 727.

358. Bonnie Rochman, *The Risks (and Rewards) of Pills and Pregnancy*, TIME, June 8, 2009, available at <http://www.time.com/time/magazine/article/0,9171,1901482-1,00.html>.