

ENCOURAGING MATERNAL SACRIFICE: HOW REGULATIONS GOVERNING THE CONSUMPTION OF PHARMACEUTICALS DURING PREGNANCY PRIORITIZE FETAL SAFETY OVER MATERNAL HEALTH AND AUTONOMY

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ABSTRACT

Pregnant women are routinely faced with the stressful decision of whether to consume needed medications during their pregnancies. Because the risks associated with pharmaceutical drug consumption during pregnancy are largely unknown, pregnant women both inadvertently consume dangerous medications and avoid needed drugs. Both outcomes are harmful to pregnant women and their fetuses.

This unparalleled lack of drug safety information is a result of ill-conceived, paternalistic regulations in two areas of the law: regulations governing ethical research in human subjects and regulations that dictate the required labels on drugs. The former categorizes pregnant women as “vulnerable” and thus precludes them from most medical research. The result is that ninety-one percent of drugs lack any reliable safety information for pregnant consumers. The latter currently requires all drug labels to encourage drug avoidance during pregnancy, despite ample evidence that avoiding needed medications can harm pregnant women. On June 30, 2015, new pregnancy labeling regulations took effect. Though these regulations make important improvements, they continue to treat pregnant women unlike any population, including other unique subpopulations, such as children. As a result, the new regulations do not fix the problem of over-warning pregnant women about the risks of drug consumption.

This article questions the legitimacy of both regulations and suggests three reforms for how to improve access to vital safety information: (1) amend the regulations governing ethical research in human subjects to reclassify pregnant women as non-vulnerable adults; (2) create incentives to generate safety data in pregnant women by granting a period of market exclusivity for drug companies that invest in this research; and (3) make the FDA pregnancy labeling regulations consistent with the routine FDA practice of requiring the display of balanced, human data on risk.

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INTRODUCTION

There is an extensive regulatory landscape surrounding the development of pharmaceutical drugs. These regulations aim to protect both the ultimate consumers of drugs and the participants of medical research—research that is required to generate the drug safety evidence necessary to protect consumers. These regulations treat pregnant women in a paternalistic manner. Medical research involving human subjects is governed by institutional review boards (“IRBs”). Under the current official IRB regulations, which are governed by federal regulation,¹ pregnant women are considered a “vulnerable population”—i.e., more susceptible to coercion—and are therefore functionally prevented from participating in medical research protocols that are available to other adults.²

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1. Protection of Human Subjects, 45 C.F.R. pt. 46 (2013).

2. *Id.* § 46.201–09; *see also* 73 Fed. Reg. 30,831, 30,840–41 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201) (“Except for the few products developed to treat conditions unique to

This categorization has greatly chilled medical research on pregnant women, with the result that hardly any evidence exists regarding a drug's safety in pregnant women or fetuses.³ Furthermore, under the U.S. Food and Drug Administration's ("FDA") current pregnancy labeling regulations,⁴ this lack of information is used to discourage pregnant women from taking medications due to their unknown risk of fetal harm.⁵ This unknown risk to the fetus is not balanced against the known harms that women and fetuses face when needed medications are avoided.⁶ These labeling regulations are much more conservative than what is required for other subpopulations, such as children.⁷

In tandem, these two sets of regulations have serious consequences for pregnant women. Women continue to need and consume pharmaceutical drugs during pregnancy, but must make their medication decisions with insufficient information as to the relative risks.⁸ This creates a Catch-22 in which the lack of

pregnancy, prescription drugs are not tested in pregnant women prior to their approval. Therefore, human data concerning a drug's effect(s) on pregnant women and their offspring almost never come from controlled clinical trials.").

3. For a critical view, see Anne Drapkin Lyerly, Margaret Olivia Little & Ruth Faden, *The Second Wave: Toward Responsible Inclusion of Pregnant Women in Research*, 1 INT'L J. FEMINIST APPROACHES TO BIOETHICS 5 (2008) [hereinafter *The Second Wave*]; Kate Greenwood, *The Mysteries of Pregnancy: The Role of Law in Solving the Problem of Unknown but Knowable Maternal-Fetal Medication Risk*, 79 U. CIN. L. REV. 267 (2011); Anne Drapkin Lyerly, Margaret Olivia Little & Ruth R. Faden, *Pregnancy and Clinical Research*, HASTINGS CTR. REPORT. Nov.–Dec. 2008, at back cover [hereinafter *Pregnancy and Clinical Research*]; Anne Drapkin Lyerly, Margaret Olivia Little & Ruth R. Faden, *Reframing the Framework: Toward Fair Inclusion of Pregnant Women as Participants in Research*, 11 AM. J. BIOETHICS 50 (2011) [hereinafter *Reframing the Framework*]; Margaret Olivia Little, Anne Drapkin Lyerly & Ruth R. Faden, *Pregnant Women & Medical Research: A Moral Imperative*, 2 BIOETHICA FORUM 60, 61–62 (2009) [hereinafter *A Moral Imperative*]; CTR. FOR BIOLOGICS EVALUATION & RESEARCH, FOOD & DRUG ADMIN., REVIEWER GUIDANCE EVALUATING THE RISKS OF DRUG EXPOSURE IN HUMAN PREGNANCIES, 3 (2005) [hereinafter REVIEWER GUIDANCE], available at <http://www.fda.gov/downloads/scienceresearch/specialtopics/womenshealthresearch/ucm133359.pdf> ("Consequently, when a drug is first marketed there are usually no human data on the effects of in utero drug exposure. The only data on fetal effects initially available in the product labeling usually comes from animal reproductive toxicology studies.").

4. 21 C.F.R. § 201.57(c)(9)(i)(A)(1)–(5) (2014).

5. *Id.*

6. *Id.*

7. See generally 21 C.F.R. § 201.57 (2014) (imposing regulation requirements for various subpopulations).

8. 73 Fed. Reg. at 30,841; see also REVIEWER GUIDANCE, *supra* note 3, at 3 ("Despite the lack of information on the safety of drug use during pregnancy, most pregnant women likely will be exposed to drugs. Fetal exposure can occur before a woman knows she is pregnant. Some women enter pregnancy with medical conditions that require continuing drug therapy. New medical problems may develop during, or old ones may be exacerbated by, pregnancy."). Some studies estimate that as many as seventy percent of women from 2006 to 2008 used at least one prescription drug during their pregnancy. See, e.g., Allen A. Mitchell, Suzanne M. Gilboa, Martha M. Werler, Katherine E. Kelley, Carol Louik, Sonia Hernández-Díaz & Nat'l Birth Defects Prevention Study, *Medication Use During Pregnancy, With Particular Focus On Prescription Drugs: 1976-2008*, 205 AM. J. OBSTETRICS & GYNECOLOGY 51.e1, 51.e4 (2011); see also David W. Kaufman, Judith P. Kelly, Lynn Rosenberg, Theresa E. Anderson & Allen A. Mitchell, *Recent*

reliable data forces pregnant women in need of medication to choose between two potentially risky options: avoid needed medications altogether or consume potentially risky drugs. On the one hand, avoiding needed medications during pregnancy can cause negative health consequences for both pregnant women and their fetuses.⁹ On the other, given that both pregnant women and their fetuses metabolize drugs differently from other adults, drug consumption during pregnancy can cause adverse reactions in both parties.¹⁰ This dilemma, at best, can cause significant anxiety for pregnant women choosing whether to consume medications;¹¹ at worst, it can cause blind decision-making, which can lead to physical harm of the pregnant woman and/or fetus.¹²

This article argues that the regulation of pregnant women in medical research and FDA labeling has created a system in which pregnant women—and, by consequence, their fetuses—are unprotected from drug risks. Pregnant women are not more susceptible to coercion than other adults, and should not be classified as a vulnerable population within the IRB regulations. They should be given equal opportunity to participate in any research protocol that meets the standard criteria for ethical adult research as established in 45 C.F.R. § 46.111. Imposing more stringent regulations on pregnant women is based on paternalistic notions that value the protection of the fetus over the pregnant woman's health, autonomy, and well-being. Furthermore, these regulations ignore the fact that the health of the pregnant woman and fetus are linked. To the extent that a pregnant woman suffers adverse health effects that result from insufficient safety information, her fetus may as well.¹³

The unfortunate consequence is that pregnant women regularly ingest drugs whose risks are unknown because it is too unpalatable to enroll them in medical research where they would also be exposed to unknown risks. Unlike the risks assumed in the research context, the risks pregnant women assume from using drugs off-label in the clinical setting are not accompanied by the benefit of generating safety data that would improve public health in the future.

Part I of this article explores how the IRB regulations, which limit and define ethical research in human subjects,¹⁴ undermine the autonomy of pregnant

Patterns of Medication Use in the Ambulatory Adult Population of the United States, 287 J. AM. MED. ASS'N 337 (2002) (concluding that nearly fifty percent of women used at least one prescription drug during their pregnancy and seven percent used five or more). See *supra* note 3 for various references regarding the lack of drug safety information in pregnancy.

9. See *The Second Wave*, *supra* note 3, at 6–7.

10. *Id.* at 8–9.

11. Women experience anxiety about using pharmaceuticals during pregnancy, in part due to an overestimation of the risks of drug consumption in pregnancy. See REVIEWER GUIDANCE, *supra* note 3, at 3 (“This exaggerated fear could lead to termination of a wanted pregnancy or to unnecessary withholding of needed drug therapy during pregnancy.”).

12. See *infra* Part I.B.

13. See *The Second Wave*, *supra* note 3; Greenwood, *supra* note 3, at 268; *A Moral Imperative*, *supra* note 3. For further discussion, see *infra* Part I.B.

14. 45 C.F.R. §§ 46.101–46.505 (2013).

women by preventing them from consenting to medical research due to their perceived vulnerability. It explains that pregnant women are not vulnerable to coercion and that classifying them as such harms the very group the regulations intend to protect. Part II examines the consequences of the FDA's pregnancy labeling regulations, which govern drug-consumption warnings for pregnant women. It first analyzes the current FDA pregnancy labeling regulations,¹⁵ and concludes that the required pregnancy warnings are overly cautious, present unreliable data derived from animal research, and exclusively focus on fetal risk. Part II.B then explores the new pregnancy labeling regulations,¹⁶ which were proposed in 2008 and finalized in December 2014.¹⁷ The regulations, which become effective in June 2015 and must be implemented by 2020,¹⁸ make important improvements; however, they remain overly cautious, focus predominantly on fetal risk, and increase reliance on animal data. Ultimately, they will not fix the real problem: the need for an unbiased presentation of human data.

Part III suggests a three-part solution: (1) remove pregnant women from the vulnerable population category in the IRB regulations, which will eliminate unnecessary barriers to their participation in research. This would demonstrate trust in the ability of pregnant women to make reasonable choices for themselves and their fetuses. (2) Create financial incentives to generate this data by granting a three-month period of market exclusivity as is done in the pediatric context. This will encourage drug companies to invest in this research. And (3) alter the pregnancy labeling requirements to mirror other populations so that reliable human data is presented neutrally and pregnant women can make informed choices.

I.

THE HARMFUL OVERREGULATION OF PREGNANT WOMEN IN MEDICAL RESEARCH

Before a pharmaceutical can enter the market, drug companies must overcome many scientific and regulatory barriers. Drug companies must first perform years of pre-clinical research in animals to justify research in humans.¹⁹

15. 21 C.F.R. § 201.57(c)(9)(i)(A)(1)–(5) (2014).

16. 73 Fed. Reg. 30,831 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

17. 79 Fed. Reg. 72,064 (proposed Dec. 4, 2014) (to be codified at 21 C.F.R. pt. 201).

18. *Id.* at 72,064, 72,095–72,096.

19. OFFICE FOR HUMAN RESEARCH PROTS., U.S. DEP'T OF HEALTH & HUMAN SERVS., INST. REVIEW BD. GUIDEBOOK, ch. 6 (2d ed. 1993), available at http://www.hhs.gov/ohrp/archive/irb/irb_chapter6.htm [hereinafter GUIDEBOOK] (describing the relationship between animal studies, Investigational New Drug Applications, and phase one clinical trials in the "Overview" section). For information on the average length of time pre-clinical studies take, see Judy Stone, *Molecules to Medicine: Clinical Trials for Beginners*, SCI. AM. (Oct. 6, 2011), <http://blogs.scientificamerican.com/guest-blog/2011/10/06/molecules-to-medicine-clinical-trials-for-beginners/>.

Once clinical research in human participants is warranted, researchers must submit their proposed human research protocols to IRBs, which review the research to determine whether or not the research is ethical.²⁰ IRB approval is time-consuming and expensive. In one study, the process of obtaining IRB approval for a multi-site research protocol cost researchers more than \$56,000 (seventeen percent of the total research grant)²¹ and took 4,680 hours over 798 days.²² Adding to this cost is the fact that each drug must pass through three phases of clinical trials, with IRB approval required at each phase.²³ In total, it can take a drug company a decade or more to generate the necessary human data to submit a New Drug Application to the FDA for approval.²⁴

Federal law requires that IRBs approve all medical research in human subjects before the research begins.²⁵ IRBs are generally housed within a research institution and review medical research proposals according to federal guidelines that define ethical research.²⁶ 45 C.F.R. § 46.111(a) (“Subpart A”) outlines seven criteria necessary for IRB approval of research in human subjects, including both vulnerable and non-vulnerable populations. This section requires that: (1) risks to subjects are minimized; (2) risks to subjects are reasonable in relation to anticipated benefits; (3) selection of subjects is equitable; (4) informed consent is sought from each prospective subject (defined in greater detail in 45 C.F.R. § 46.116); (5) informed consent is appropriately documented; (6) when appropriate, the collected data is monitored to ensure the safety of subjects; and (7) the privacy of subjects is protected.²⁷ If the IRB believes that a research protocol fails to meet any of these seven requirements, it can reject the proposal outright, which would terminate the research project immediately, or accept the protocol only after the research team makes the revisions it requests.²⁸

In addition to the criteria listed in Subpart A, research in pregnant women must also meet the stricter regulations found in 45 C.F.R. § 46.204 (“Subpart

20. National Research Act, Pub. L. No. 93-348, 88 Stat. 342 (1974); 45 C.F.R. § 46.103 (2014).

21. Keith Humphreys, Jodie Trafton & Todd H. Wagner, *The Cost of Institutional Review Board Procedures in Multicenter Observational Research*, 139 ANNALS OF INTERNAL MED. 77, 77 (2003).

22. Lee A. Green, Julie C. Lowery, Christine P. Kowalski & Leon Wyszewianski, *Impact of Institutional Review Board Practice Variation on Observational Health Services Research*, 41 HEALTH SERVS. RESEARCH 214, 219-20 (2006).

23. *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm> (last updated Nov. 16, 2014).

24. See Stone, *supra* note 19.

25. National Research Act; 45 C.F.R. § 46.103.

26. See ERIN D. WILLIAMS, CONG. RESEARCH SERV., FEDERAL PROTECTION FOR HUMAN RESEARCH SUBJECTS: AN ANALYSIS OF THE COMMON RULE AND ITS INTERACTIONS WITH FDA REGULATIONS AND THE HIPAA PRIVACY RULE 2 (2005), available at <http://www.fas.org/sgp/crs/misc/RL32909.pdf>.

27. 45 C.F.R. § 46.111(a) (2013).

28. *Id.*

B”), entitled “Additional Protections for Pregnant Women, Human Fetuses and Neonates Involved in Research.”²⁹ Part I.A of this article examines the regulatory hurdles of Subpart B, which a researcher must overcome to conduct research involving pregnant women or fetuses. Part I.B of this article discusses the practical implications of these regulations: pregnant women are largely excluded from all medical research and, as a result, there is little drug-safety information available for this group.³⁰ Because pregnant women continue to consume drugs despite the lack of safety information, the result is that these regulations, although ostensibly protective, generate unnecessary risk and harm to women and fetuses.³¹ Part I.C of this article explores whether or not this harm is justified, and concludes that it is not. The justification rests on the categorization of pregnant women as “vulnerable to coercion or undue influence,”³² yet there is no reason to believe pregnancy clouds a woman’s decision-making capacity or makes her unable to resist pressure. Because the justification for these regulations is ill conceived, the harm is unwarranted.

Feminist bioethicists have previously criticized the consequences of excluding pregnant women from medical research³³; however, despite these arguments, there have not been legislative or regulatory efforts to alter this practice. Part I aims to look at the problem through a different disciplinary perspective by bringing this issue to light in the legal literature.

A. *The Regulatory Criteria for Ethical Research in Pregnant Women*

The criteria outlined in Subpart A establish the baseline requirements for ethical research in human subjects. Research in pregnant women, however, is also subject to the more extensive regulations outlined in Subpart B.³⁴ These regulations require that the proposed research have the potential to benefit the pregnant woman directly.³⁵ If the research does not have the prospect of direct benefit, a pregnant woman is prohibited from enrolling in the study if it poses a

29. 45 C.F.R. § 46.204 (2014).

30. See *supra* discussion accompanying note 3; W. Y. Lo & J. M. Friedman, *Teratogenicity of Recently Introduced Medications in Human Pregnancy*, OBSTETRICS & GYNECOLOGY, 465, 468 (2002) (finding that 91.2% of drug treatments approved in the US between 1980 and 2000 did not have human safety data on use during pregnancy).

31. See *infra* discussion in Part I.B.

32. 45 C.F.R. § 46.111(b). The term vulnerable is not defined in the regulations. However, it is clear that the regulators assumed some sort of cognitive vulnerability by, at one point, referring to it as a vulnerability to coercion or undue influence: “When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.” *Id.*

33. See *supra* discussion accompanying note 3.

34. 45 C.F.R. § 46.201–207 (2014). Subpart C (45 C.F.R. § 46.301–306) relates to prisoners and Subpart D (45 C.F.R. § 46.401–409) relates to children.

35. § 46.204(b).

“greater than minimal risk” to her fetus.³⁶ The purpose of the research must be the development of important biomedical knowledge that cannot be obtained by any other means.³⁷ Overall, Subpart B contains ten provisions; however, two of them—Sections (a) and (b)—are primarily responsible for the lack of research in pregnant women.³⁸

First, when scientifically appropriate, the IRB reviewing a research proposal must have access to preclinical trials in pregnant animals to assess the risk to fetuses and pregnant women.³⁹ The IRB must also have access to data on clinical trials in non-pregnant women.⁴⁰ This poses two obstacles to conducting trials in pregnant women. First, drug companies must invest in costly studies of pregnant animals.⁴¹ Second, pregnant women can be enrolled only after clinical trials have already been conducted in non-pregnant women. This two-trial requirement is also expensive.⁴² Because there is no regulatory requirement to generate information on drug safety in pregnancy,⁴³ and drug companies are not forced to compete according to this measurement,⁴⁴ there is no financial incentive for drug companies to spend the money investing in this research.⁴⁵

36. § 46.204(d).

37. *Id.*; see also Christine Grady & Colleen Denny, *Research Involving Women*, in THE OXFORD TEXTBOOK OF CLINICAL RESEARCH ETHICS 409 (Ezekiel J. Emanuel, Christine Grady, Robert A. Crouch, Reidar K. Lie, Franklin G. Miller & David Wendler eds., 2008).

38. § 46.204(a)–(b).

39. § 46.204(a).

40. *Id.*

41. While drug companies must already invest in animal studies to be granted an Investigational New Drug Application from the FDA so that they can begin their research in humans, there is no requirement to do pre-clinical studies on pregnant animals for every drug. 21 C.F.R. § 312.23(a)(8) (2014); GUIDEBOOK, *supra* note 19. The cost of such additional studies is high, especially given the difficulty in obtaining pregnant animals. See EUROPEAN FED’N OF PHARM. INDUS. & ASS’NS, MAKING SENSE OF ANIMAL RESEARCH 7 (2008), available at http://www.animalresearchforlife.eu/Making_sense_of_animal_research.

42. In 2007, pharmaceutical and biotechnology companies spent nearly sixty billion dollars on drug research. *Clinical Trials Facts and Figures*, CTR. FOR INFO. & STUDY ON CLINICAL RESEARCH PARTICIPATION, https://www.cisr.org/wp-content/uploads/2014/03/cisr_data_archive_facts_and_figures_for_health_professionals.pdf (last visited Dec. 8, 2013). Clinical trials now constitute sixty percent of drug development costs. Furthermore, to the extent the clinical trials on pregnant women or research on pregnant animals delayed bringing a drug to market, it would cost a drug company \$8 million per day.

43. It is only required when seeking to produce a drug intended for use in that population. 21 C.F.R. § 312.23(a)(8)(ii)(a) (2014) (“Depending on the nature of the drug and the phase of the investigation, the description is to include the results of acute, subacute, and chronic toxicity tests; tests of the drug’s effects on reproduction and the developing fetus.”). See generally 21 C.F.R. § 312.23(a)(8).

44. Given that drug companies as a whole do not produce this information, and at this point, pregnant women have not demanded it, there has been no market pressure to invest in these studies so as to gain a competitive market edge.

45. *A Moral Imperative*, *supra* note 3, at 63 (“All will agree that regulations should restrict when and how research can be conducted on pregnant women. But without any legislative or regulatory pressure to include pregnant women in some fashion, a powerful, systemic incentive

Second, Subpart B requires that any risk posed to the fetus must be outweighed by the prospect of benefit to either the fetus or the pregnant woman; otherwise, the risk must be minimal (defined as not greater than the risks encountered in everyday activities or routine procedures)⁴⁶ and necessary to obtain scientific knowledge.⁴⁷ Practically speaking, any risk that a drug poses to a fetus will be interpreted as beyond minimal risk—a fetus encounters very few risks from everyday activities or routine procedures, and any unknown harmful effects of a drug could produce serious complications in a developing fetus.⁴⁸ Thus, the issue debated by IRBs is whether the potential for maternal benefit might outweigh the potential for fetal risk. This is extremely difficult to quantify and the result is that IRBs tend to overestimate fetal risk and underestimate maternal benefit.⁴⁹

Subpart B regulations are only concerned with fetal, not maternal risk⁵⁰—if an experimental therapy poses only risks to the pregnant woman and not the fetus, then the regulations do not require that the risk be outweighed by potential

structure is established. It is easier for researchers to side-step the regulatory burden that pregnant women currently represent by excluding them wholesale from all research, including research that imposes no risk, or risk that is clearly reasonable in its context. Without changing the burdens of justification, all the incentives to the research community line up in favor of simply ignoring pregnant women.”).

46. Minimal risk is defined as follows: “A risk is minimal where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.” GUIDEBOOK, *supra* note 19, at ch. 6. For a list of research methods presumed to pose minimal risk, see *Office for Human Research Protections (OHRP) - Categories of Research*, U.S. DEP’T HEALTH & HUMAN SERVS., <http://www.hhs.gov/ohrp/policy/expedited98.html> (last visited Dec. 8, 2013).

47. 45 C.F.R. § 46.204(b) (2013).

48. Despite a very low probability that a drug could cause birth defects, the nature of birth defects, and their possible preventability, means that IRBs and government agencies take them very seriously. See REVIEWER GUIDANCE, *supra* note 3, at 2 (“About 4 percent (1/28) of babies are born each year with a major birth defect or congenital malformation Chemically induced birth defects, including those associated with drug exposure, probably account for less than 1 percent of all birth defects Of the thousands of drugs available, only about 20 drugs or groups of drugs . . . are recognized as having an increased risk of developmental abnormalities when used clinically in humans. However, since few drugs have been systematically studied to identify their full range of possible teratogenic risks, we cannot assume that current knowledge is complete. The identification of a drug’s teratogenic potential is important because drug-induced adverse fetal effects are potentially preventable.”); see also GUIDEBOOK, *supra* note 19.

49. Toby Schonfeld, *The Perils of Protection: Vulnerability and Women in Clinical Research*, 34 THEORETICAL MEDICINE & BIOETHICS 189, 196 (2013). For an examination of the overestimation of risk for medical interventions in the clinical setting for pregnant women, see Anne Drapkin Lyerly, Lisa M. Mitchell, Elizabeth Mitchell Armstrong, Rebecca Kukla, Miriam Kuppermann & Margaret Olivia Little, *Risk and the Pregnant Body*, 39 HASTINGS CTR. REPORT. 34, 34–35 (2009).

50. Nowhere in 45 C.F.R. § 46.204(b) is maternal risk mentioned—maternal benefit must be balanced against fetal risk. Compare this to 45 C.F.R. § 46.111(a)(2), where the benefit to the adult must be balanced against the risk to the adult.

for direct benefit. Instead, the general standard for risk, found in Subpart A applies to pregnant women as it applies generally to all adults. It requires that risk be “reasonable in relation to anticipated benefits [to her].”⁵¹ This results in a dichotomy: risks to the fetus are treated as grave while risks to the pregnant woman are treated as due course. This is despite a similar lack of knowledge about how a given drug could affect the pregnant woman, who could also have an unknown adverse drug response as a consequence of pregnancy.⁵²

There are other substantive differences between the Subpart B regulations, which govern research in pregnant women, and the Subpart A regulations, which govern research in all adults. Any risk posed by research in pregnant women must be “the least possible” to achieve the objectives of that research.⁵³ By contrast, the risks of research in other adults must simply be minimized.⁵⁴ This stricter language further contributes to IRBs’ reluctance to approve research in pregnant women. The regulations also require a pregnant woman’s informed consent, as that term is defined in Subpart A.⁵⁵ This is the same informed-consent requirement that applies to other adults.⁵⁶ However, there are two additional components that alter the informed consent process. First, if the research participation is solely to benefit the health of the fetus, the pregnant woman’s partner must also consent to the woman’s research participation.⁵⁷ This is unless the partner “is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.”⁵⁸ Second, whoever consents to the research must be informed of any foreseeable impact on the fetus.⁵⁹ Pregnant minors must provide consent according to the regulations for children, as well as obtain parental permission.⁶⁰ The regulations also include three prohibitions related to abortion: researchers cannot provide inducements for abortion, advise on whether, how, or when to terminate a pregnancy, or determine fetal viability.⁶¹

51. 45 C.F.R. § 46.111(a)(2) (2013).

52. *The Second Wave*, *supra* note 3, at 7; *A Moral Imperative*, *supra* note 3, at 61.

53. 45 C.F.R. § 46.204(c) (2013) (emphasis added).

54. § 46.111(a)(1).

55. § 46.204(d).

56. § 46.111(a)(4).

57. § 46.204(e).

58. *Id.* This article’s description of § 46.204(e) deviates from the exact language of the regulation to avoid hetero-normativity. The exact text of the regulation uses the male pronoun to refer to a pregnant woman’s partner and discusses the necessity of obtaining the “father’s consent.”

59. § 46.204(f).

60. § 46.204(g).

61. § 46.204(h)–(j).

Regulations governing research in pregnant women are significantly more burdensome than those that regulate research in other adults.⁶² They are costly and create regulatory hurdles for researchers desiring to conduct research in this population. While Subpart B does not prohibit research in pregnant women, and seems reasonable on its face, it has widespread consequences.⁶³ Part I.B of this article explores these practical implications and the harmful impact they have had on pregnant women and fetuses.

B. Consequences of the IRB Regulations

The burden these regulations impose is reflected in the infrequency with which trials in pregnant women occur. The reality is that “many researchers and IRBs continue to regard pregnancy as a near-automatic cause for exclusion.”⁶⁴ Thus, even if a drug company is willing to pursue the additional cost associated with research in pregnant women (by first testing drugs in pregnant animals and repeating trials after they have been conducted in non-pregnant women), IRBs will make it very difficult to conduct this research. As a result, only 0.7 percent of drugs have been approved for use in pregnant women,⁶⁵ and 91.2 percent of drugs lack any human safety data on consumption during pregnancy.⁶⁶

This lack of data is particularly concerning because pregnant women and their fetuses process and metabolize drugs differently from other adults.⁶⁷ This is in large part due to the physical changes that accompany pregnancy as:

Pregnancy alters the impact of sex differences on absorption, distribution, metabolism, and excretion of drugs—often times in ways that are both dramatic and difficult to predict. Pregnancy-related changes in the gastrointestinal tract, the cardiovascular system, the kidneys, and other organs may profoundly alter the ways that drugs are processed by the body (pharmacokinetics) or the ways that drugs act on the body (pharmacodynamics).⁶⁸

Case studies have documented the impact of this phenomenon. For instance, in one study, a pregnant woman undergoing chemotherapy metabolized and excreted the drug “so quickly and thoroughly that the drug never approached a

62. Compare 45 C.F.R. § 46.111(a) (denoting the criteria for IRB approval of research in general), with § 46.204 (denoting the more stringent requirements for research involving pregnant women or fetuses).

63. See *supra* note 3 for a discussion about the lack of drug safety data in pregnant women.

64. *The Second Wave*, *supra* note 3, at 6.

65. See J.M. Friedman, *Report of the Teratology Society Public Affairs Committee Symposium on FDA Classification of Drugs*, 48 *TERATOLOGY* 5 (1993).

66. Lo & Friedman, *supra* note 30, at 468.

67. See *The Second Wave*, *supra* note 3, at 8–9; *A Moral Imperative*, *supra* note 3, at 61; Lucy S. Hodge & Timothy S. Tracy, *Alterations in Drug Disposition During Pregnancy: Implications for Drug Therapy*, 3 *INFORMAL HEALTHCARE* 557 (2007).

68. *The Second Wave*, *supra* note 3, at 8.

therapeutic range, despite the fact that she and the fetus were exposed to its toxicities.”⁶⁹ A similar effect has been demonstrated with drugs treating diabetes in pregnancy—the dose provided created side effects without providing therapeutic benefits.⁷⁰ Because pregnancy can dramatically change a woman’s drug response, treatments may need to be altered.⁷¹ The lack of drug safety information related to pregnancy makes it difficult to determine the appropriate dosage.

Fetuses also suffer from this lack of information. In the 1950s and 1960s, for example, pregnant women were routinely prescribed thalidomide. Though the FDA never approved the drug for use in the United States, it was legally available for use as a sedative in other countries.⁷² Doctors quickly began to prescribe thalidomide to pregnant women off-label⁷³ for morning sickness despite a lack of safety information.⁷⁴ As a result, “more than 10,000 children in 46 countries were born with malformations or missing limbs.”⁷⁵ The thalidomide case study is distinct in that the FDA never approved the drug in the United States. This example nevertheless demonstrates the possible outcomes associated with off-label drug use in pregnancy, which occurs routinely in the United States and is exacerbated by a lack of safety information for pregnant women.

A more recent example is that of antidepressants, which physicians prescribe during pregnancy for good reason, though without adequate information. We are only now learning of the potential effects of these drugs on the fetus, such as correlations with autism, newborn behavioral syndrome, persistent pulmonary hypertension, and heart conduction problems.⁷⁶ Another noteworthy example is that of assisted reproductive technologies. In a recent compilation of studies, the risk of birth defects was shown to be 1.36 times greater in children conceived through assisted reproductive technologies than in spontaneously conceived children.⁷⁷

69. *Id.* at 8–9.

70. Anne Drapkin Lyerly, Margaret Olivia Little & Ruth R. Faden, *The National Children’s Study: A Golden Opportunity to Advance the Health of Pregnant Women*, 99 AM. J. PUB. HEALTH 1742, 1742 (2009).

71. See *The Second Wave*, *supra* note 3; *A Moral Imperative*, *supra* note 3, at 61; Hodge & Tracy, *supra* note 67; Lyerly, Little & Faden, *supra* note 70, at 1742–43.

72. Bara Fintel, Athena T. Samaras & Edison Carias, *The Thalidomide Tragedy: Lessons For Drug Safety And Regulation*, HELIX MAGAZINE (July 28, 2009), <https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation>.

73. *Id.*

74. Rachel Hajar, *Animal Testing and Medicine*, 12 HEART VIEWS 42, 42 (2011).

75. *Id.*

76. See Adam Urato, *Commentary: More Bad News on Antidepressants and Pregnancy*, COMMON HEALTH (June 12, 2012, 7:43 AM), <http://commonhealth.wbur.org/2012/06/antidepressants-pregnancy>.

77. Yan Jia, Li-hong Geng & Ying Zhong, *Birth Defects in Assisted Reproductive Technology and Spontaneously Conceived Children: A Meta-Analysis*, 24 J. REPRODUCTION & CONTRACEPTION 237, 240 (2013).

However, the solution does not involve a strict avoidance of medications. Forgoing treatment out of concern for fetal harm can also result in disastrous consequences. For instance, the reticence to use CT scans during pregnancy has led to a delayed diagnosis of appendicitis which can lead to the rupture of the pregnant woman's appendix and miscarriage.⁷⁸ In a nationwide study during the 2009 outbreak of the H1N1 virus, "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."⁷⁹ Pregnant women who suffer from depression may also face serious complications when they fail to take needed medications. These complications include "premature birth, low birth weight, fetal growth restriction, and postnatal complications. [Depression] also is associated with decreased social support, poor weight gain, and alcohol and drug use, all of which adversely affect outcomes for women and infants alike."⁸⁰ Without information regarding drug safety, physicians cannot reliably inform pregnant women about whether it is safer to avoid or consume certain medications. This creates a treacherous dilemma for pregnant women: either avoid needed medications that might improve their own and/or their fetus's health, or use medication off-label without fully understanding its health effects.

In practice, our society allows pregnant women to consent to the risks of off-label drug use on behalf of themselves and their fetuses every day. In light of this, it seems the FDA should trust women to make similar risk calculations when they consider whether to participate in medical research. Given the sheer number of women consuming pharmaceuticals in the clinical setting, the risks associated with clinical off-label drug use are broader and more widespread than those potentially involved with small number of pregnant women participating in research.⁸¹ Unlike the risks assumed by pregnant women in the research context, clinical off-label drug use in pregnancy lacks the added benefit of generating data that would eventually reduce overall risks by determining which drugs are safe for consumption in pregnancy, and which drugs pose risks.⁸²

The only way to remove these risks in the medical context is to generate data: "a pregnant woman is not just a woman with a bigger belly If we are to treat pregnant women's illnesses effectively—something crucial to the health of *both* pregnant women and that of the children they may bear—we must study medications in pregnant women."⁸³ Since seventy percent of pregnant women

78. See Lyerly, Mitchell, Armstrong, Harris, Kukla, Kuppermann & Little, *supra* note 49.

79. Greenwood, *supra* note 3, at 269.

80. *The Second Wave*, *supra* note 3, at 11.

81. Instead of exposing small groups of pregnant women to these risks for small periods of time through clinical studies, we expose all women to these risks without any end in sight.

82. Clinical trials produce reliable evidence upon which to base clinical decisions. Pregnant women taking these medications on their own produce no evidence for future benefit.

83. *The Second Wave*, *supra* note 3, at 9.

use prescription drugs every year,⁸⁴ more robust data could greatly improve maternal and fetal outcomes. Given these negative consequences, the remaining question is whether requiring stricter standards for research in pregnant women is justified. The following Part explores this question in more detail.

C. The Categorization of Pregnant Women as Vulnerable is Unjustified

The regulations governing IRB approval of research classify pregnant women as a group “likely to be vulnerable to coercion or undue influence.”⁸⁵ This is a designation that pregnant women share with four other groups: children, prisoners, mentally disabled persons, and economically or educationally disadvantaged persons.⁸⁶ Additional safeguards “to protect the rights and welfare of these subjects” are required before the IRB can approve a study involving any of these groups.⁸⁷ Only three of the five populations, however, were considered vulnerable enough to warrant additional, defined regulations: prisoners,⁸⁸ children,⁸⁹ and a group referred to as “pregnant women, human fetuses, and neonates.”⁹⁰ Before research can occur in these three populations, an IRB must approve the research protocol according to a higher standard than the baseline protections established in 45 C.F.R. § 46.111. Research involving pregnant women must meet the additional requirements of Subpart B.⁹¹ By contrast, research involving the mentally disabled or the economically or educationally disadvantaged is not subject to stricter regulations apart from the safeguards required in § 46.111(b).⁹²

Children, prisoners, and pregnant women are considered vulnerable because it is assumed that these groups are particularly susceptible to coercion.⁹³ Under

84. See Mitchell, Gilboa, Werler, Kelley, Louik, Hernández-Díaz & Nat'l Birth Defects Prevention Study, *supra* note 8.

85. 45 C.F.R. § 46.111(b) (2014).

86. *Id.*

87. *Id.*

88. § 46.301–06.

89. § 46.401–07.

90. § 46.201–09.

91. *Id.*

92. § 46.111(b).

93. See Karen J. Schwenger, *Protecting Vulnerable Subjects in Clinical Research: Children, Pregnant Women, Prisoners, and Employees*, 53 RESPIRATORY CARE 1342, 1343 (2008); MARY C. RUOF, VULNERABILITY, VULNERABLE POPULATIONS, AND POLICY 2 (2001), available at <https://bioethics.georgetown.edu/publications/scopenotes/sn44.pdf> (“In clinical research, the term vulnerable generally is applied to individuals who are unable to give informed consent or who are susceptible to coercion.”); 45 C.F.R. § 46.111(b) (“When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects.”).

this theory, these groups may be unable to resist the incentives or pressure to participate in research, and must be excluded from it for their own protection.⁹⁴

Pregnant women should not be designated as a vulnerable group. Children and prisoners are truly susceptible to coercion, and these groups do need additional protections.⁹⁵ Given the inherent power imbalance between state and prisoner, and parent and child, it may not be possible for a child or a prisoner to consent freely to participation in medical research.⁹⁶ Parents and prison officials have the power to punish and reward. This power can pressure the weaker party to participate in research even if the dominant party never uses her power: “The vulnerability creating feature here is the extent to which consent or permission to participate in a study reflects the desires and values of the surrogate decision maker rather than of the potential participant herself.”⁹⁷ Pregnant women, on the other hand, are not subject to this sort of coercive pressure.

Other laws that recognize the vulnerability of children and prisoners—specifically, their inability to give free and informed consent—do not extend the same status to pregnant women.⁹⁸ For instance, rape laws, where consent is fundamental to the legality of conduct, generally treat prisoners and children as incapable of consenting to sexual activity.⁹⁹ Thus, it is a felony for an adult to

94. See GUIDEBOOK, *supra* note 19.

95. Schonfeld, *supra* note 49, at 196 (“Juridic vulnerability obtains in situations in which others have legal authority over the decisional processes of someone. Common examples of these social situations are parents over children, wardens over prisoners, and military commanders over enlisted soldiers.”).

96. *Id.*

97. *Id.*

98. See GUIDEBOOK, *supra* note 19 (“The circumstances common in prisons create environments in which the offer to participate in research is necessarily coercive or creates a undue influence in favor of participation. To the extent that living conditions in prison are bad and the provision of health care is minimal or even nonexistent, the lack of control allowed prisoners and the desire to obtain the advantages offered to those who agree to participate may preclude their ability to weigh fairly the risks and benefits involved in participation.”); Michelle Roth-Cline & Robert M. Nelson, *Parental Permission and Child Assent in Research on Children*, 86 *YALE J. BIOLOGY & MED.* 291, 291–92 (“For research involving children, both of these safeguards are modified given the vulnerability of children to undue influence or coercion. There are limits set to the risks that a child may be exposed to in research that does not offer a prospect of direct benefit and limits set to the justification of risks that a child may be exposed to in research that offers a prospect of direct benefit. As discussed below, these additional requirements for research involving children arise from the difficulty in applying a model of self-determination to parental permission and child assent.”).

99. See NAT’L INST. OF CORR. & THE PROJECT ON ADDRESSING PRISON RAPE AT WASHINGTON COLLEGE OF LAW, FIFTY STATE SURVEY OF STATE CRIMINAL LAWS ADDRESSING THE SEXUAL EXPLOITATION OF MINORS (2006) [hereinafter LAWS ADDRESSING THE SEXUAL EXPLOITATION OF MINORS], available at <http://static.nicic.gov/Library/021769.pdf>; see also THE PROJECT ON ADDRESSING PRISON RAPE AT WASHINGTON COLLEGE OF LAW, FIFTY-STATE SURVEY OF CRIMINAL LAWS PROHIBITING SEXUAL ABUSE OF INDIVIDUALS IN CUSTODY (2011) [hereinafter LAWS PROHIBITING SEXUAL ABUSE].

have sex with a child or a prison official to have sex with a prisoner.¹⁰⁰ Because the sexual activity cannot be separated from the coercive power dynamic that exists between adults and children or guards and prisoners, this is a strict liability crime regardless of any proclaimed “consent.”¹⁰¹ The policy justification is nearly identical in medical research—consent to medical research participation that could be based on the pressure to appease an authority figure should not be validated. Given the extensive policy justifications for protecting these two classes of people against coercive influences, it is legitimate to limit their research participation to studies, which IRBs have determined to be in their best interests.

Pregnant women, on the other hand, are fully autonomous adults, wholly capable of giving informed consent. In fact, due to a history of discrimination in certain contexts like employment, anti-discrimination statutes were enacted to ensure that women were not inappropriately deemed incapable during their pregnancies.¹⁰² Despite the physical impairments that can accompany some pregnancies, pregnant women do not face any diminished mental or intellectual capacity. Unlike prisoners and children, pregnant women are legally capable of consenting to sexual activity. Although historical notions of a pregnant woman’s frailty exist,¹⁰³ these notions were discredited decades ago. Regarding their ability to consent, pregnant women are not prevented from entering into contracts, creating trusts, wills, or advanced directives, or consenting to other kinds of risks, like military participation or medical interventions.¹⁰⁴ In fact, the regulations provide little justification for categorizing pregnant women as vulnerable.¹⁰⁵

100. LAWS ADDRESSING THE SEXUAL EXPLOITATION OF MINORS, *supra* note 99; LAWS PROHIBITING SEXUAL ABUSE, *supra* note 99; Patricia J. Falk, *Rape by Fraud and Rape by Coercion*, 64 BROOK. L. REV. 39, 101–07 (1998).

101. See Michelle Oberman, *Turning Girls Into Women: Reevaluating Modern Statutory Rape Law*, 85 NW. J. CRIM. L. & CRIMINOLOGY 15 (1994).

102. Pregnancy Discrimination Act, Pub. L. No. 95–555, 92 Stat. 2076 (1978).

103. See generally CLARE HANSON, A CULTURAL HISTORY OF PREGNANCY: PREGNANCY, MEDICINE AND CULTURE, 1750–2000, 23–36, 51–71 (2004) (providing a cultural history of pregnancy between 1750 and 2000).

104. The one important exception to this general rule is in the context of medical decisions thought by some to not be in the best interest of the fetus. For instance, cases exist in which physicians override the pregnant woman’s wishes and perform a caesarian section. Lisa Collier Cool, *Could You Be Forced To Have A C-Section?*, NAT’L ADVOCATES FOR PREGNANT WOMEN (2005), http://www.advocatesforpregnantwomen.org/articles/forced_c-section.htm.

105. Grady & Denny, *supra* note 37, at 408 (“This label [‘vulnerable’], however, does seem to confuse what entity is vulnerable and at risk. There does seem to be a widely held intuition among both researchers and the general public that pregnant women require greater protection than do non-pregnant human beings, but support for that intuition is often unclear, particularly in the research setting. Most regulation and guidelines offer no explanations for these special protective measures, and those that do usually refer to the risk of fetal rather than maternal harm during research participation.”).

More likely, the classification of pregnant women as a vulnerable population is a pretext for the state's protection of the fetus.¹⁰⁶ There is historical evidence to suspect that Subpart B was really an attempt to express concern for the unborn: "The vocal pro-life community, galvanized in the wake of the U.S. Supreme Court's 1973 *Roe v. Wade* decision, expressed concern for the unborn fetuses by pushing for stringent limits on women's research participation."¹⁰⁷ Dr. Charles McCarthy has argued that the debate over abortion rights in the wake of *Roe* is one of three events that profoundly altered the public's view on medical research.¹⁰⁸ Additional evidence for this contention can be found in the text of Subpart B, where three of the ten conditions of IRB approval of research in pregnant women involve limitations on abortion.¹⁰⁹ This is an odd context in which to insert restrictions on abortion funding; unlike women seeking abortions, there is no reason to think pregnant research subjects are attempting to end their pregnancies. Indeed, participating in medical research may indicate a pregnant woman's desire to improve health outcomes both for herself and for her fetus. Nevertheless, it is impossible to divorce the issue of medical research on pregnant women from the context of the ongoing abortion debate.

The strongest justification for the restrictions in Subpart B is based not on the need to protect the pregnant woman from coercion, but on the inability of the fetus to give informed consent. Because the fetus cannot consent to the research—including any side effects that might develop after the fetus is born—the government undertakes an obligation to protect the fetus from medical research in a similar way to how it protects children. However, this overlooks three vital differences between fetuses and children: (1) the fetus's health is directly linked to the pregnant woman's health while in utero. Thus, any medical benefit to the pregnant woman is likely to improve fetal health outcomes. (2) Once the child and woman are separate beings, increasing regulatory protections for children in research comes at no cost to the mother. Regulatory protections of the fetus, however, do create costs for the pregnant woman. She may lose the potential to benefit from medical research, both as a participant and as a pregnant

106. *Id.*; Schonfeld, *supra* note 49; GUIDEBOOK, *supra* note 19 ("The fetus has a unique and inextricable relationship to the mother. It cannot consent to be a research subject. These circumstances have aroused lengthy public debate on the ethics of fetal research, and led to special federal regulations that guide IRB deliberations about fetal research [45 C.F.R. 46 Subpart B]. The fetus may also be an indirect subject of research when women who may be pregnant participate. Research involving pregnant women is also regulated by 45 C.F.R. 46 Subpart B.").

107. Grady & Denny, *supra* note 37 (citing *Roe v. Wade*, 410 U.S. 113 (1973)); see also Charles R. McCarthy, *Historical Background of Clinical Trials Involving Women and Minorities*, 69 ACAD. MED. 695, 696 (1994) ("The highly emotional abortion debate, including its connotations, had a chilling effect on research involving women of childbearing potential and human fetuses.").

108. McCarthy, *supra* note 107, at 696. In addition to *Roe*, Dr. McCarthy also cites the revelation of the Tuskegee syphilis experiment and the irrational exuberance surrounding President Nixon's "war on cancer" as events that "tended to deter participation in clinical trials by a wide spectrum of persons who were potential research subjects." *Id.*

109. 45 C.F.R. § 46.204(h)–(j) (2013).

woman trying to make informed medical decisions in her daily life. These costs should not be ignored. (3) We allow pregnant women to consent to unknown risks on behalf of their fetuses in the medical context all the time. When doctors prescribe drugs to treat illnesses in pregnant women, the prescription is almost always off-label.¹¹⁰ In this sense, pregnant women conduct a sort of experimentation on themselves—with risks similar to that of IRB research, but without any of the safeguards.¹¹¹

Though the fetus is unable to consent, its interests in this context cannot be regarded as wholly separate from the pregnant woman's interests. The fetus's welfare is directly attached to the welfare of the woman: "Physically, the woman and fetus are interconnected, the health or illness of one influencing the same in the other. More than that, the future wellbeing of each is, in the usual case, deeply connected. Children are affected by their parents' health and happiness; parents are affected by their children's well-being."¹¹² Consider the examples discussed above: delaying medical treatment for H1N1 or appendicitis in pregnant women not only harmed the woman, but the fetus as well.¹¹³ Unhealthy pregnant women increase the likelihood of health complications for their fetuses and untreated illness can cause miscarriages.¹¹⁴ For instance, depression in pregnancy is correlated with low birth weight,¹¹⁵ pre-term delivery, low Apgar score, fetal growth retardation, neonatal irritability, and behavioral problems.¹¹⁶ Regardless, depression often remains untreated for fear of drug risks, even though "this fear is not evidence-based, but rather a cautionary response attributable to a lack of randomized controlled trials in pregnant women . . ."¹¹⁷ Other examples include a higher incidence of fetal cardiac malformations if the

110. See *The Second Wave*, *supra* note 3, at 7.

111. This is different in the pediatric context, where off-label pediatric usage is less prevalent because more drugs have been tested and approved by the FDA for use in children. "[I]n 2009, more than 60 percent of the drugs used for both adults and children that were in the Physician's Desk Reference—a drug information resource for physicians and other health professionals—had specific information on pediatric use . . ." *Database Is One-Stop Resource on Kids' Medications*, U.S. FOOD & DRUG ADMIN. (May 22, 2012), <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm305040.htm>. However, 91.2 percent of drug treatments approved between 1980 and 2000 did not have any human safety data on consumption during pregnancy. See Lo & Friedman, *supra* note 30, at 465.

112. *The Second Wave*, *supra* note 3, at 14.

113. See Lyerly, Mitchell, Armstrong, Harris, Kukla, Kuppermann & Little, *supra* note 49; *The Second Wave*, *supra* note 3, at 12; see also Greenwood, *supra* note 3, at 268.

114. See *The Second Wave*, *supra* note 3, at 12; see also Little, Lyerly & Faden, *supra* note 3.

115. See A. S. Khashan, C. Everard, L. M. E. McCowan, G. Dekker, R. Moss-Morris, P. N. Baker, L. Poston, J. J. Walker & L. C. Kenny, *Second-Trimester Maternal Distress Increases the Risk of Small for Gestational Age*, 44 PSYCHOL. MED. 2799, 2806 (2014).

116. Alison Reminick, Stacy Cohen & Adrienne Einarson, *Managing Depression During Pregnancy*, 9 WOMEN'S HEALTH 527, 529 (2013).

117. *Id.* at 527.

woman has diabetes while pregnant,¹¹⁸ higher risk of neurological complications if the woman has a Cytomegalovirus infection while pregnant,¹¹⁹ higher risk of low birth weight and preterm delivery if the woman has asthma while pregnant,¹²⁰ and higher risk of miscarriage and perinatal morbidity and mortality if the woman has various autoimmune diseases, such as lupus, anti-phospholipid syndrome, multiple sclerosis, and type-one diabetes.¹²¹ Fetal and maternal outcomes can be improved if these conditions are treated during pregnancy,¹²² though many physicians are reluctant to do so.

Given this correlation with the health of the pregnant woman and the health of the fetus, it is unclear whether purported fetal-maternal conflict is legitimate in most cases, or, at the very least, whether it is serious enough to justify government interference. Though medical research is different from clinical treatment, any health benefit achieved through medical research in the pregnant woman could also improve the health outcomes in the fetus, despite potentially exposing it to risks. The risks involved in permitting pregnant women to participate in medical research are important and worth serious consideration, but the reality is that fetal birth defects as a result of drug exposure are uncommon.¹²³ This insight is only more powerful given that these protective regulations, which in practical effect ban pregnant women from research, harm fetuses in the long run. When pregnant women choose to avoid medications needed to treat illness, their health can worsen, which can also diminish their fetuses' health outcomes. Conversely, if pregnant women consume physician-prescribed medications during their pregnancies that carry unknown dangers, this could lead to fetal defects and cause future disabilities.¹²⁴ If women had drug-safety information produced from clinical trials, maternal and fetal health would

118. See Avisá Tabib, Nooshin Shirzad, Sara Sheikhabaei, Sara Mohammadi, Mostafa Qorbani, Vahid Haghpanah, Farzaneh Abbasi, Shirin Hasani-Ranjbar & Ramin Baghaei-Tehrani, *Cardiac Malformations in Fetuses of Gestational and Pre Gestational Diabetic Mothers*, 23 IRAN J. OF PEDIATRICS 664, 666 (2013).

119. See Karen B. Fowler, Sergio Stagno, Robert F. Pass, William J. Britt, Thomas J. Boll & Charles A. Alford, *The Outcome of Congenital Cytomegalovirus Infection in Relation to Maternal Antibody Status*, 326 NEW ENG. J. MED. 663, 663 (1992).

120. See Diego J. Maselli, Sandra G. Adams, Jay I. Peters & Stephanie M. Levine, *Management of Asthma During Pregnancy*, 7 THERAPEUTIC ADVANCES RESPIRATORY DISEASE 87, 88 (2014).

121. See Andrea T. Borchers, *The Implications of Autoimmunity and Pregnancy*, 34 J. AUTOIMMUNITY J287 (2010).

122. See Reminick, Cohen & Einarson, *supra* note 116; Maselli, Adams, Peters & Levine *supra* note 120, at 97; Borchers, *supra* note 121, at J296–97.

123. See REVIEWER GUIDANCE, *supra* note 3, at 2 (“Chemically induced birth defects, including those associated with drug exposure, probably account for less than 1 percent of all birth defects; few drugs are proven human teratogens at clinical doses. Of the thousands of drugs available, only about twenty drugs or groups of drugs (most being anticonvulsants, antineoplastics, or retinoids) are recognized as having an increased risk of developmental abnormalities when used clinically in humans.” (citation omitted)). Even thalidomide is not dangerous when prescribed at the right time of pregnancy. *Id.*

124. See *The Second Wave*, *supra* note 3, at 10–11; Little, Lysterly & Faden, *supra* note 3.

improve because physicians would know when to prescribe and when to avoid medications in pregnancy. Though more information might not always provide perfect guidance, it would permit pregnant women to make more informed decisions based on their own values. Pregnant women should be trusted to understand the relative risks of participating in research and to decide what is best for themselves and their fetuses.

Finally, certain scholars have employed an autonomy-based critique of the designation of a fetus as separate from the pregnant woman.¹²⁵ Seeing the fetus as a distinct patient has led some physicians to inappropriately prioritize fetal health over maternal health to the detriment of both.¹²⁶ Pregnant women should be seen and respected for their own health beyond their capacity to create a fetal environment. This requires physicians to focus on the woman as the patient; if the fetus becomes the focus, the woman becomes lost in her pregnancy. Although this criticism was made in the context of medical treatment, as opposed to research, the point remains salient in the research context, where pregnant women are denied the opportunity to benefit due to concerns about the fetus:

First is the worry that such a designation [of a fetus as a patient] may encourage a tendency to think of the fetus as separate from the pregnant woman, obscuring the physical and social relationship between pregnant woman and fetus, the ways that maternal and fetal physiologies and welfare are linked, and perhaps most problematically, the woman herself [T]he designation of [the fetus as a] ‘patient’ may make it easier to think about the pregnant woman herself as an environment rather than a patient in her own right.¹²⁷

Denying pregnant women the ability to participate in medical research solely because they are pregnant seriously limits their personal autonomy to make their own choices. This should only be permitted when there is a strong justification, which Subpart B lacks.

Rationales for excluding pregnant women from research—their susceptibility to coercion, inherent vulnerability, or eagerness to prioritize their own interests above their fetus’s—are based on antiquated and harmful stereotypes that should be eliminated. Society ought to grant pregnant women the autonomy to make complicated risk calculations, even when those involve potential fetal harm. Though the overwhelming majority of mothers would likely only participate in research if they believed it could benefit both themselves and their fetuses, this is not the only instance in which it might be ethical for pregnant women to participate. For instance, there are times when a pregnant

125. Anne Drapkin Lyerly, Margaret Olivia Little & Ruth Faden, *A Critique of the ‘Fetus as Patient,’* 8 AM. J. BIOETHICS 42 (2008).

126. *See id.* at 43.

127. *Id.* (internal citation omitted).

woman's needs are so great that it might be appropriate for her to participate in medical research despite a likelihood that the fetus could be harmed.¹²⁸ This is true especially in the context of experimental therapy for life-threatening conditions, where risks to the fetus should be balanced against the possibility of the woman's death while pregnant (and the subsequent death of the fetus).

Ultimately, the IRB regulations that attempt to protect pregnant women and their fetuses yield an odd result; in order to protect fetuses from the risks of medical research, both fetuses and pregnant women are subjected to similar risks through exposure to untested medications. By crafting regulations that have systematically excluded pregnant women from medical research for their own protection, the government created a system in which pregnant women are routinely exposed to risks without any of the public health benefits. Protecting people from this exact harm—the risks of untested drugs—is one of the reasons the IRB system was created.¹²⁹

Not only do these regulations permit pregnant women to assume the risks of research without any benefits, they also manufacture bad science. Currently, the best source of information on the risks of drugs is pregnancy exposure registries and other post-approval research methods.¹³⁰ Pregnancy exposure registries collect health information from pregnant women who consume drugs after FDA approval; women enroll when they begin taking medications, before any complications have arisen.¹³¹ If a complication with the medication does arise, then the pregnant women report it to the registry.¹³² While these registries provide needed information for guidance data-deprived population,¹³³ and are the most scientifically accurate post-approval monitoring device,¹³⁴ the reliable information they generate is limited.¹³⁵

FDA approval of a new drug is only based on randomized, double-blind, placebo-controlled clinical trials—this high standard ensures that misleading

128. See Little, Lyerly & Faden, *supra* note 3, at 61–62.

129. *About FDA, What We Do*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/aboutfda/whatwedo/> (last updated Aug. 5, 2014).

130. 73 Fed. Reg. 30,831, 30,840–41 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201) (“Therefore, human data concerning a drug’s effect(s) on pregnant women and their offspring almost never come from controlled clinical trials Sources that may contribute to an evaluation of whether a drug increases the risk of developmental abnormalities include pregnancy exposure registries, cohort studies, case-control studies, case series, and case reports.”).

131. See Dianne L. Kennedy, Kathleen Uhl & Sandra L. Kweder, *Pregnancy Exposure Registries*, 27 DRUG SAFETY 215, 217 (2004).

132. *Id.*

133. *Id.*; 73 Fed. Reg. at 30,839–41.

134. *Id.*

135. See Kennedy, Uhl & Kweder, *supra* note 131 (explaining the scientific limitations of pregnancy exposure registries and identifying them as best used as a hypothesis-generating tool or to identify major risks).

information will not be produced as a result of bad study design.¹³⁶ If the FDA believes that only this gold standard of clinical research can produce reliable information, the agency should not sanction¹³⁷ pregnancy exposure registries as a way to circumvent these reliable, clinical trials. Exposure registries are helpful once reliable data exists, but they are insufficient to determine the baseline safety standard.

The regulations governing ethics approval of medical research involving pregnant women force pregnant women and doctors to make decisions based on unreliable science: information generated by animal studies¹³⁸ or observation through pregnancy exposure registries.¹³⁹ Both pregnant women and their fetuses would benefit from the generation of safety data through reliable clinical trials conducted in pregnant women.

II.

FDA LABELING REGULATIONS BIAS PREGNANT WOMEN AGAINST DRUG CONSUMPTION

Once clinical trials are completed, a drug company will apply for FDA approval. FDA approval is the final step before a drug can enter the market. The FDA will only approve a new drug after clinical trials in human subjects demonstrate that the drug is safe and effective.¹⁴⁰ Drugs are approved only for specific uses and any off-label promotion by a drug company can be prosecuted.¹⁴¹ For this reason, the approval of a drug also involves the review of

136. 21 U.S.C. § 355(d)(1)–(5) (2012); 21 C.F.R. § 314.126 (2014); Suzanne White Junod, *FDA and Clinical Trials: A Short Story*, U.S. FOOD & DRUG ADMIN., available at <http://www.fda.gov/AboutFDA/WhatWeDo/History/Overviews/ucm304485.htm> (last updated July, 7, 2014) (“Although several kinds of randomized controlled trial methodologies can be useful to researchers and regulators, ultimately, it was the randomized, double-blinded, placebo controlled experiment which became the standard by which most other experimental methods were judged, and it has often subsequently been referred to as the “gold” standard for clinical trial methodology.”).

137. As discussed in Part II.B., the FDA’s proposed and final labeling regulation includes a focus on pregnancy exposure registries as a way to generate this new information. 73 Fed. Reg. at 30,839–41; 79 Fed. Reg. 72,064, 72,069 (proposed Dec. 4, 2014) (to be codified at 21 C.F.R. pt 201).

138. See *infra* note 190 for a discussion on the reliability of animal studies.

139. See *supra* notes 130–137.

140. 21 U.S.C. § 355(d) (2012).

141. U.S. Dep’t of Justice Press Release, Inspections, Compliance, Enforcement, and Criminal Investigations, FDA (Nov. 4, 2013), available at <http://www.fda.gov/iceci/criminalinvestigations/ucm375816.htm> (“Under the FDCA, a pharmaceutical company must specify the intended uses of a drug in its new drug application to the FDA. Before approval, the FDA must determine that the drug is safe and effective for those specified uses. Once the drug is approved, if the company intends a different use and then introduces the drug into interstate commerce for that new, unapproved use, the drug becomes misbranded. The unapproved use is also known as an “off-label” use because it is not included in the drug’s FDA-approved labeling.”).

its labeling to ensure that the label provides accurate information on risks and promotes proper use.¹⁴²

Once a drug company has completed the necessary clinical trials, it submits a New Drug Application (“NDA”) to the FDA for approval. Many considerations go into the FDA’s decision whether to approve a drug. In addition to reviewing the clinical data to ensure the drug is safe and effective,¹⁴³ the FDA also regulates the labels that accompany drugs.¹⁴⁴ It is important to note that any information a company wants to include in marketing materials must be based on approved product labeling as, “FDA-approved product labeling is the foundation upon which all promotional information about a drug is based. In other words, promotional labeling and advertising may not contain information or claims not asserted in the FDA-approved product labeling.”¹⁴⁵

Under current regulations, all non-exempt drug labels must include warnings specific to pregnant women.¹⁴⁶ The regulations categorize drugs into five pregnancy categories, each of which requires a different label to be placed on the drug.¹⁴⁷ The categories are based on available risk information. As clinical data based on research in pregnant women is rare, risks established only through research in pregnant animals often dictate the class to which the drug is assigned.¹⁴⁸ Due to substantial criticism of the current regulatory framework, the FDA proposed new pregnancy labeling regulations in 2008 to modify its existing

142. 21 C.F.R. § 201.56-57 (regulating the labeling reviewed during the FDA approval process). See MATTHEW BENDER & LAW JOURNAL PRESS, REGULATION OF PHARMACEUTICAL MANUFACTURERS § 1.07(2)(a) & (3) (2012) (discussing the requirements of the approved product labeling and their importance as the benchmark for what constitutes off-label use).

143. 21 U.S.C. § 355(d)(1)–(5).

144. The Federal Food, Drug and Cosmetic Act (“FDCA”) defines *label* as a “display of written, printed, or graphic matter upon the immediate container of any article . . .” Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 321(k) (2012). “The term ‘immediate container’ does not include package liners.” *Device Labeling: Introduction to Medical Device Labeling, Label vs. Labeling*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/DeviceLaDevice/> (last updated Jan. 8, 2013). Labeling has been further defined by FDA regulations, which created a list of items that fit within the definition of labeling. 21 C.F.R. § 202.1(l)(2) (2014) (“Brochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the ‘Physicians Desk Reference’) for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor are hereby determined to be labeling as defined in section 201(m) of the act.”).

145. BENDER & LAW JOURNAL PRESS, *supra* note 142, at § 107(2)(a).

146. See 21 C.F.R. § 201.57(c)(9)(i) (2014). Exempt labels are those where the drug is “absorbed systemically” and “is not known to have a potential for indirect harm to the fetus.”

147. See § 201.57(c)(9)(i)(A)(1)–(5).

148. *Id.*

regulations.¹⁴⁹ The final rule came out in December 2014, and took effect on June 30, 2015.¹⁵⁰ However, the final rule will not be fully implemented until 2020.¹⁵¹ The next Part explores the previous regulations and the new, final pregnancy labeling regulations. It concludes that the previous regulations were inadequate, and though the new regulations improve on key issues, they still fail to treat pregnancy labeling consistently with other labeling regulations, such as pediatric labeling.

A. Previous Pregnancy Labeling Regulations Prioritized Fetal Harm over Maternal Health, Failed to Present Neutral Information, and Required the Presentation of Unreliable Data

Previous pregnancy labeling regulations are currently being phased out. However, because the final rule will not be fully implemented until 2020, understanding the previous regulations is highly relevant to understanding the current and ongoing changes in the law. This is especially true in light of the fact that many of the changes to the pregnancy labeling regulations result from criticisms of the previous regulations. The requirement to include pregnancy warnings on the labeling of drugs is found in two identically worded provisions of the Code of Federal Regulations.¹⁵² 21 C.F.R. § 201.57(c)(9)(i) governs drugs submitted for FDA approval after 2006, while 21 C.F.R. § 201.80(f) governs drugs submitted to the FDA for approval before 2006.¹⁵³ The regulations required that all drugs “not absorbed systemically and . . . not known to have a potential for indirect harm to the fetus,”¹⁵⁴ must have one of five warning labels.¹⁵⁵ The available risk information regarding a certain drug correlates with a class category: A, B, C, D, or X. (See Table One below.) All drugs in a given class had to contain the assigned language related to the respective sub-category as part of their labeling.¹⁵⁶

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

150. 79 Fed. Reg. 72,064 (proposed Dec. 4, 2014) (to be codified at 21 C.F.R. pt. 201).

151. *Id.* at 72,095–96.

152. *See* 21 C.F.R. § 201.57(c)(9)(i) (2014) (governing drugs submitted to the FDA for approval after 2006); Specific Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products; Older Drugs Not Described in § 201.56(b)(1), 21 C.F.R. § 201.80(f) (2012) (governing drugs submitted to the FDA for approval prior to 2006). The two regulations are identical but for the dates of the drugs they govern. In later citations I will only cite to 21 C.F.R. § 201.57(c)(9)(i) since this is the regulation related to post-2006 drugs.

153. *Id.*

154. 21 C.F.R. § 201.57(c)(9)(i).

155. § 201.57(c)(9)(i)(A)(1)–(5).

156. § 201.57(c)(9)(i)(A).

Table One: Description of the Pregnancy Labeling Requirements in Effect from 2006 – 2015

<i>Class</i>	<i>Available Risk Evidence</i>	<i>Required Warning</i>
A ¹⁵⁷	Adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)	Studies in pregnant women have not shown that (name of drug) increases the risk of fetal abnormalities if administered during the first (second, third, or all) trimester(s) of pregnancy. If this drug is used during pregnancy, the possibility of fetal harm appears remote. Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed.
B ¹⁵⁸	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women	Reproduction studies have been performed in (kind(s) of animal(s)) at doses up to (x) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to (name of drug). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used in pregnancy only if clearly needed.
	Animal reproduction studies have shown an adverse effect (other than decrease in fertility), but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of a risk in later trimesters)	Reproduction studies in (kind(s) of animal(s)) have shown (describe findings) at (x) times the human dose. Studies in pregnant women, however, have not shown that (name of drug) increases the risk of abnormalities when administered during the first (second, third, or all) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (name of drug) should be used during pregnancy only if clearly needed.
C ¹⁵⁹	Animal reproduction studies have shown an adverse effect on the fetus, there are no adequate and well-controlled studies in humans, and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks	(Name of drug) has been shown to be teratogenic (or to have an embryocidal effect or other adverse effect) in (name(s) of species) when given in doses (x) times the human dose. There are no adequate and well-controlled studies in pregnant women. (Name of

157. § 201.57(c)(9)(i)(A)(1).

158. § 201.57(c)(9)(i)(A)(2).

159. § 201.57(c)(9)(i)(A)(3).

		drug) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
	There are no animal reproduction studies and no adequate and well-controlled studies in humans	Animal reproduction studies have not been conducted with (name of drug). It is also not known whether (name of drug) can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. (Name of drug) should be given to a pregnant woman only if clearly needed.
D ¹⁶⁰	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)	(Name of drug) can cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.
X ¹⁶¹	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit (for example, safer drugs or other forms of therapy are available)	(Name of drug) may (can) cause fetal harm when administered to a pregnant woman. (Describe the human data and any pertinent animal data.) (Name of drug) is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus.

These labeling instructions are inadequate for many reasons, the most significant being that they are unnecessarily precautionous. Even for Class A drugs—drugs in which clinical trials in pregnant women and pregnant animals have failed to demonstrate harm¹⁶²—the labeling must include the following warning: “Because studies cannot rule out the possibility of harm, however, (name of drug) should be used during pregnancy only if clearly needed.”¹⁶³ Even if a drug is able to gain Class A status—a status only 0.7% of drugs hold¹⁶⁴—the drug label must contain a warning against taking the drug unless doing so is clearly needed. Such a precaution is unjustified. The risk of harm associated with drug consumption can never be conclusively ruled out whether or not one is pregnant. Not only do all drugs carry some side effects that are not worth enduring unless the drug is needed, but also it is not unheard of for FDA-

160. § 201.57(c)(9)(i)(A)(4).

161. § 201.57(c)(9)(i)(A)(5).

162. § 201.57(c)(9)(i)(A)(1).

163. *Id.*

164. See Friedman, *supra* note 65.

approved drugs, which have undergone rigorous clinical trials in human subjects, to be removed from the market due to serious safety concerns.¹⁶⁵ Yet, despite the inability of the FDA to conclusively rule out potential drug harm, the FDA does not require such cautious labeling in non-pregnancy contexts. If it did, every pharmaceutical would be required to contain a warning label that discouraged drug consumption unless clearly needed, as all drugs have risks that are not worth enduring without an indication that the drug is needed. Because drug consumption should always be avoided unless clearly needed, the language on the pregnancy labeling was wholly unnecessary. No doctor would prescribe a medication and subject her patient to risk unless the patient needed the drug. While this general practice is not unique to pregnancy, pregnancy labeling regulations are the only place in which such a warning is required,¹⁶⁶ indicating that the FDA is singling out pregnant women by encouraging them to avoid needed medications.

A comparison with the pediatric labeling requirements underscores how unusual and paternalistic pregnancy warnings are. Children can also have different drug responses than the general population.¹⁶⁷ Therefore, like medication intended for pregnant women and fetuses pediatric drug consumption requires unique labeling.¹⁶⁸ As in pregnant women, testing drugs in children has also been very difficult to accomplish due, in large part, to the regulations guiding IRB approval in this population.¹⁶⁹ Because children are also considered vulnerable, research on them must meet the more extensive requirements of another subpart (Subpart D) in addition to the baseline requirements found in Subpart A.¹⁷⁰ This has led to a similar lack of information on drug safety in children.¹⁷¹ Unlike the pregnant population, however, this was viewed as “poor

165. See, e.g., *Vioxx Recall Information*, DRUGWATCH, <http://www.drugwatch.com/vioxx/recall/> (last visited July 11, 2013); *Drug Recalls*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/DrugSafety/DrugRecalls/default.htm> (last visited Oct. 15, 2014); *Sequence of Events with VIOXX, Since Opening of IND*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4090B1_04_E-FDA-TAB-C.htm (last visited Dec. 19, 2014).

166. See generally § 201.57.

167. See *Drug Research and Children*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/Drugs/ResourcesForYou/Consumers/ucm143565.htm> (last visited Oct. 19, 2014) (citing a physician explaining that children are not simply “small adults”); *Children, FDA Basics*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/aboutfda/transparency/basics/ucm319792.htm> (last visited November 2, 2014) (explaining that children’s bodies break drugs down differently than adults).

168. See *Drug Research and Children*, *supra* note 167 (discussing how increasing clinical trials testing drugs’ effects on children has resulted in changing labeling information regarding appropriate dosing for children).

169. See *Additional Protections for Children Involved as Subjects in Research*, 45 C.F.R. § 46.401–09 (2013).

170. *Id.*

171. See Donna R. Rivera & Abraham G. Hartzema, *Pediatric Exclusivity: Evolving Legislation and Novel Complexities within Pediatric Therapeutic Development*, 48(3) ANNALS OF PHARMACOLOGY 369, 371 (2013) (posing hypotheticals as to why clinical trials in children are rare with the consequence of there being a lack of information on drug safety in children).

public policy,” and Congress acted to fix this problem through a new provision of the Food and Drug Administration Modernization Act (“FDAMA”), discussed in more depth below.¹⁷² While this legislation improved the problem significantly,¹⁷³ some approved drugs still lack pediatric-risk information and the FDA at times faces similar difficulties in requiring pediatric warnings without reliable data. Pediatric labeling bears several distinctions from pregnancy labeling. Pediatric drugs are not placed into classes, and the contents of pediatric labels are much less cautious.¹⁷⁴ Unlike pregnancy labeling, these regulations simply note that when clinical trials have been conducted in the pediatric population that support a specific pediatric indication, that information must be included under the “Indications and Usage” section and appropriate pediatric dosage information must be given under the “Dosage and Administration” section.¹⁷⁵ While any clinical findings of risk must be provided in the “Pediatric Use” subsection on the labeling,¹⁷⁶ there is no requirement that the labeling must include a blanket warning to abstain from consumption if possible.¹⁷⁷

Furthermore, when *no* safety information exists in this population, the warning required by the FDA still does not encourage avoidance of these drugs. Instead, the following warning must be given: “Safety and effectiveness in pediatric patients have not been established.”¹⁷⁸ Even if pediatric studies have demonstrated a potential for harm in the pediatric population, the FDA does not require a warning against drug consumption. These risks are treated similarly to risks established for healthy adults—they must simply be noted in the “Contraindications” or “Warnings and Precautions” sections.¹⁷⁹ In other words, the FDA permits drugs that are known to be risky to children to contain less precautionous labeling than drugs tested in pregnant women without any demonstration of risk. This kind of overprotective language found in the

172. *Id.* at 370 (explaining the patent extension incentive offered to pharmaceutical companies by the FDAMA if they conducted FDA-approved pediatric trials according to certain standards). This provision is discussed in greater depth *infra* Part III.

173. *Id.* at 375. (“This legislation has been successful because the FDA reports that 425 pediatric studies have been conducted as of December 2012. This speaks well to the successful efforts of the program to increase pediatric medication knowledge.”).

174. Compare 21 C.F.R. § 201.57(c)(9)(iv) (2014) (labeling requirements for pediatric risk), with 21 C.F.R. § 201.57(c)(9)(i) (labeling requirements for fetal risk).

175. § 201.57(c)(9)(iv)(B).

176. *Id.* (“The ‘Pediatric use’ subsection must cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug.”).

177. *Id.*

178. § 201.57(c)(9)(iv)(F).

179. *Id.* (“If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk must be made, generally in the ‘Contraindications’ or ‘Warnings and Precautions’ section.”).

pregnancy labeling cannot be found anywhere else in the FDA's labeling regulations.¹⁸⁰

The previous pregnancy labeling regulations also painted an incomplete picture for readers in that they focused exclusively on fetal (as opposed to maternal) risks from drug consumption.¹⁸¹ The regulations encouraged pregnant women to avoid drugs and failed to present information on the risks associated with drug avoidance.¹⁸² When an unknown, or under-evaluated, risk exists for the pregnant woman herself, the FDA did not require any additional precautions, and women were left with little information regarding their own health risks.¹⁸³ Given that pregnant women can also have an abnormal response to drugs and lack information on how their own bodies will process them,¹⁸⁴ these regulations were inappropriately lopsided. Warnings for fetuses are much more protective than those for children;¹⁸⁵ yet pregnant women, who are also susceptible to increased drug risks, received no warnings for their own safety.¹⁸⁶ Pregnant women are therefore under-warned about risks to themselves, and over-warned about risks to their fetus.

This recommendation to avoid drug consumption might be more reasonable if there were no risks associated with drug avoidance. As explored in Part I, however, this excess caution can be very dangerous to women and, by consequence, their fetuses.¹⁸⁷ Despite this known harm, the current pregnancy labeling regulations do not display any information about the potential harm of avoiding needed medications to balance the uniquely precautionary warnings.¹⁸⁸ Risk information on avoiding medication is necessary in this context to balance out the overly cautious labeling required by the FDA. After reading warning labels, pregnant women may be left with the impression that taking medications could be risky, while avoiding medications will be safe. Pregnant women deserve all available information to make well-informed decisions. This one-sided story is another example of how the regulations prioritize fetal health while ignoring the pregnant woman. With all available information, many women would continue to choose drug avoidance; yet failing to provide women with this data inappropriately biases decision-making.

The final criticism of the previous pregnancy labeling regulations explored in this Part is the use of animal data on warning labels. While animal studies are

180. See § 201.57.

181. § 201.57(c)(9)(i).

182. *Id.*

183. See *id.*

184. See *The Second Wave*, *supra* note 3, at 8–9.

185. Compare § 201.57(c)(9)(i) (labeling requirements for fetal risk), with § 201.57(c)(9)(iv) (labeling requirements for pediatric risk).

186. § 201.57(c)(9)(i).

187. See *supra* Part I.B.; *The Second Wave*, *supra* note 3, at 9–13; Little, Lyerly & Faden, *supra* note 3.

188. § 201.57(c)(9)(i).

included in all five pregnancy labels, the warning required for Class B drugs provides the best example of how oddly such information is displayed:

Reproduction studies in (*kind(s) of animal(s)*) have shown (*describe findings*) at (x) times the human dose. Studies in pregnant women, however, have not shown that (*name of drug*) increases the risk of abnormalities when administered during the first (*second, third, or all*) trimester(s) of pregnancy. Despite the animal findings, it would appear that the possibility of fetal harm is remote, if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, (*name of drug*) should be used during pregnancy only if clearly needed.¹⁸⁹

Despite clinical studies in pregnant women indicating a lack of harm, the warning had to have included contradicting animal studies, which are often a bad predictor of a human drug response.¹⁹⁰ Perplexingly, the animal data is displayed before human data.

One might question the use of *any* animal studies on drug labels. Animal studies have never been considered highly predictive,¹⁹¹ and indeed, the FDA requires human clinical trials before drug approval.¹⁹² For instance, when a drug lacks safety information in the pediatric context, the FDA does not mandate that animal information be used in lieu of that data.¹⁹³ Instead, they require that the label indicate that human studies have not been performed and thus risk information is unavailable.¹⁹⁴ Compare this to the pregnancy context, where 88.7 percent of drugs approved by the FDA between 2003 and 2012 contained labeling based only on animal data.¹⁹⁵

189. § 201.57(c)(9)(i)(A)(2) (Pregnancy category B).

190. The lack of clear predictability of animal studies in animals has long been demonstrated. See Gideon Koren, Anne Pastuszak & Shinya Ito, *Drugs in Pregnancy*, 338 NEW ENG. J. MED. 1128, 1131 (1998); Niall Shanks, Ray Greek & Jean Greek, *Are Animal Models Predictive for Humans?*, 4 PHIL. ETHICS & HUMAN. MED. 2 (2009); Wendy E. Wagner, *Choosing Ignorance in the Manufacture of Toxic Products*, 82 CORNELL L. REV. 773, 778–79 (1997); see also Robert Brent, *Utilization of Animal Studies to Determine the Effects and Human Risks of Environmental Toxicants (Drugs, Chemicals, and Physical Agents)*, 113 PEDIATRICS 984, 986 (2004) (explaining that animal studies are helpful in predicting a drug's response in humans, but that data from a range of other investigative approaches is required to make accurate predictions).

191. See *supra* text accompanying note 190.

192. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,840–41 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201). If these studies were sufficient, the FDA would not require extensive tests in humans.

193. See § 201.57(c)(9)(iv).

194. *Id.*

195. See Maryann Mazer-Amirshahi, Samira Samiee-Zafarghandy, George Gray & Johannes N. van den Anker, *Trends in Pregnancy Labeling and Data Quality for US-approved Pharmaceuticals*, AM. J. OBSTETRICS & GYNECOLOGY, June 7, 2014, at 1.e4.

Perhaps in the pregnancy context, requiring animal data is justified due to an overwhelming dearth of information, which may be less true of the pediatric context given various reforms discussed in Part III of this article. While this might explain the use of animal data when human data is unavailable, it is inappropriate and confusing to use animal data when contradicting human studies exist. Human data is more reliable and should always trump animal studies.¹⁹⁶ This is especially pronounced for experiments on pregnant animals, where “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.”¹⁹⁷ Other problems include “findings in a single animal species that are caused by unique drug metabolism or a mechanism of action thought not to be relevant to humans.”¹⁹⁸ This use of animal data in drug labeling is not seen anywhere else in the labeling regulations.¹⁹⁹

Overall, the current regulatory framework for pregnancy labeling fails to warn pregnant women of risks to themselves, over-warns them about risks to their fetuses, uses unreliable animal data to suggest risk, and fails to balance any fetal risk with the maternal and fetal risk of avoiding needed medications. These inadequacies demonstrate a unique lack of neutrality on behalf of the FDA. This is not the first time that questions have arisen regarding the FDA’s neutrality for politically charged issues related to reproduction. Most recently, the FDA’s failure to approve the Plan B emergency-contraception pill for girls under seventeen was struck down by courts as lacking scientific basis:

Because the Secretary’s action was politically motivated, scientifically unjustified, and contrary to agency precedent, it cannot provide a basis to sustain the denial of the Citizen Petition [T]he agency’s decision cannot withstand any degree of scrutiny, not only because of its unexplained failure to follow the FDA policies discussed above but also because of its disregard for the scientific evidence that the FDA had before it.²⁰⁰

This is noteworthy because under the *Chevron* doctrine,²⁰¹ courts typically defer to agencies’ reasonable interpretations of statutory language.

196. See *supra* text accompanying note 190.

197. Greenwood, *supra* note 3, at 284.

198. Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30,831, 30,864 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

199. See § 201.57.

200. *Tummino v. Hamburg*, 936 F. Supp. 2d 162, 192 (E.D.N.Y. 2013)); see also *Tummino v. Torti*, 603 F. Supp. 2d 519, 546 (E.D.N.Y. 2009) (“Indeed, the evidence strongly suggests that even the decision to permit the OTC sale of Plan B to women over the age of 18 was made solely to facilitate the confirmation of Dr. von Eschenbach as Commissioner of the FDA.”).

201. See *Chevron U.S.A., Inc. v. Natural Res. Def. Council, Inc.*, 467 U.S. 837, 844 (1984).

B. The Insufficiency of the 2008 Pregnancy Labeling Change Proposal and 2015 Final Rule

In May of 2008, after receiving substantial criticism of the current pregnancy labeling, the FDA proposed to amend the regulations.²⁰² The proposal was drastic. First, the FDA would cease to place drugs into categories.²⁰³ After noting that the categorization model is not used in any other context, the FDA concluded that a narrative structure would be less confusing.²⁰⁴ The FDA also recognized the inadequacy of animal data and the need, expressed most persuasively by the physician community, to have human data upon which to base proper patient counseling about risks.²⁰⁵ The proposed regulation's fix to this problem, however, was to require that pregnancy exposure registry information be placed prominently on the labeling.²⁰⁶ The hope was that more pregnant women would participate in these registries if participation information were easily accessible. Taken together, the proposed pregnancy subsection would include the following information in the order presented: "(1) Pregnancy exposure registry information (if applicable), (2) a general statement about the background risk of fetal developmental abnormalities, (3) a fetal risk summary, (4) clinical considerations, and (5) data."²⁰⁷ Furthermore, the FDA proposed that all drugs include a pregnancy subsection, not just drugs that are absorbed systemically and affect the fetus.²⁰⁸

The final rule, which took effect on June 30, 2015, in large part codified the proposals set out in 2008. As is customary, the final rule tweaked the language found in the proposed rule and made some substantive changes, but kept the main provisions intact. The main pregnancy label headings under the final rule are the following: (1) Pregnancy Exposure Registry; (2) Risk Summary; (3) Clinical Considerations; and (4) Data.²⁰⁹

The FDA's new labeling regulation is important. It makes great strides toward clarity and is a good first step toward normalizing pregnancy labeling with other kinds of FDA subpopulation labeling. This is especially true with the removal of categories and the proposal to detail risk through the traditional narrative style used by the FDA.²¹⁰ Of special note, the new regulation will require a background risk statement to be placed on all drugs.²¹¹ This

202. 73 Fed. Reg. 30,831 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

203. 73 Fed. Reg. 30,838.

204. *Id.*

205. 73 Fed. Reg. 30,840–41.

206. 73 Fed. Reg. 30,839.

207. *Id.*

208. *Id.*

209. 79 Fed. Reg. 72,064, 72,101–02 (proposed Dec. 4, 2014) (to be codified at 21 C.F.R. pt. 201).

210. *Id.* at 72,076

211. *Id.* at 72,101.

requirement requires all labeling to include information on the baseline risk of birth defect and miscarriage.²¹² In light of the fifteen-to-twenty-percent risk of spontaneous miscarriage, the 0.5-percent risk of stillbirth, and the 3.5-percent risk of birth defect in any given pregnancy,²¹³ the FDA wanted pregnant women to know that their pregnancy could have complications even if they avoided all drug consumption.²¹⁴ The final rule requires the labeling to “state the percentage range of live births in the United States with a major birth defect and the percentage range of pregnancies in the United States that end in miscarriage, regardless of drug exposure. If such information is available for the population(s) for which the drug is labeled, it must also be included.”²¹⁵ This is vital information that encourages more informed decision-making—women should know that even if they avoid all drugs, their fetus might still be born with health problems. Furthermore, it might reduce any guilt pregnant women feel if they have complications with their pregnancy after taking medications given that their use of pharmaceuticals may not have been to blame.

Other significant improvements come under the “Clinical Considerations” subheading. First, the fetal and maternal risks associated with untreated medical conditions—i.e., avoiding needed drugs—would be indicated in the labeling: “If there is a serious known or potential risk to the pregnant woman and/or the embryo/fetus associated with the disease or condition for which the drug is indicated to be used, the labeling must describe the risk.”²¹⁶ In the proposed rule, the FDA supported including this information by referencing the health risks associated with failure to treat medical conditions in pregnancy:

Of the 62 million women of childbearing age (15 to 44) in the United States (Ref. 28), more than 9 million have chronic conditions such as asthma, epilepsy, and hypertension (Ref. 29) that require ongoing treatment with prescription medicines. Failure to treat these conditions properly can have serious consequences for pregnant women and fetuses.²¹⁷

This provision is a tremendous step toward helping women to understand the risks to themselves and their fetus of avoiding needed drugs.

Another important change in the final rule is a requirement to list *maternal* risks of drug consumption that are unique to pregnancy.²¹⁸ As discussed above, pregnant women do not always process drugs in the same way as non-pregnant adults. This provision will ensure that women are aware of the risks to their own

212. *Id.*

213. 73 Fed. Reg. 30,831, 30,839 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

214. 73 Fed. Reg. 30,839.

215. 79 Fed. Reg. 72,101.

216. *Id.*

217. 73 Fed. Reg. 30,844.

218. 79 Fed. Reg. 72,101–02.

health if they take a medication.²¹⁹ It also requires the labeling to state whether or not there are available interventions to monitor or mitigate the risks of those drugs, as well as whether the drug's dose, timing, and duration of exposure could impact the maternal adverse reaction.²²⁰ These changes demonstrate that the FDA is concerned about the health impact of drugs on both the pregnant woman and the fetus, which is an important and much-needed shift.

Finally, the regulations also require more data to be presented in the labeling, and with greater detail. The fetal-risk evidence available for each drug must be placed in a subsection entitled "Data" below other pregnancy information.²²¹ The regulations also require a summary of this information in the "Risk Summary" section.²²² Both will include a description of human, animal, and pharmacological data (in that order).²²³ Notably, human data demonstrating that a drug is associated with a specific fetal developmental outcome must be compared with the potential for that developmental outcome without the drug.²²⁴ The risk summary must also indicate when there is no human risk data available.²²⁵ Finally, the new regulations have removed any blanket warning not to take the drug.²²⁶ Taken together, these changes will improve the clarity of the evidence presented to women and remove unnecessary, fear-inducing language.

While these new regulations represent a significant step forward, they include notable failures. The main one is that the regulations will continue to require all known animal data to be placed on the labeling, even when human data is available, and the animal data is low quality.²²⁷ The new regulation goes even further than the prior regulation in that it also requires pharmacology data to be displayed on the pregnancy label.²²⁸ Though any human data must be displayed first,²²⁹ human data is largely unavailable. Animal and pharmacology data is required in the Risk Summary Section and animal data is also required in the Data Section.²³⁰

Many comments to the proposed rule argued that animal data should not be included on FDA labels at all. The FDA received eleven comments (fifteen percent of the seventy-two comments²³¹ it received in total) "primarily from

219. *Id.*

220. *Id.*

221. 79 Fed. Reg. 72,102.

222. *Id.*

223. *Id.*

224. *Id.*

225. *Id.*

226. *See id.* at 72,101–02.

227. *Id.* at 72,102; *see also* discussion *supra* Part II.A.

228. 79 Fed. Reg. at 72,064; 72,0691.

229. *Id.* at 72,101.

230. *Id.* at 72,101–02.

231. *Id.* at 72,071

toxicologists, teratologists, and organizations representing toxicologists and teratologists . . . expressing strong disagreement with the proposal to use risk statements to characterize animal data.”²³² Of these eleven,

Several comments stated that the proposal to use category language to describe animal data demonstrates a misunderstanding of the function and meaning of experimental animal studies. These comments explained that although animal data can identify the potential of a therapeutic agent to cause developmental toxicity, it cannot give rise to an estimate of the probability of human harm.²³³

The FDA did not respond directly to this criticism, but noted simply that “when animal studies do not meet current standards for nonclinical developmental toxicity studies or when there are no animal data, the labeling must so state.”²³⁴ This response begs the question: if the studies do not meet current standards, then why should they be included on the labeling at all? This is especially true, given that in the FDA’s draft guidance for industry—released on the same day as the final rule—the FDA admits that it is not “possible to conclude that a drug causes an increased risk of a particular type of developmental effect based on animal data alone.”²³⁵ The inclusion of high-quality animal data is itself controversial, but including poor quality animal data on FDA drug labels is highly out of touch with the FDA’s mission.²³⁶ At the very least, the FDA should limit the presence of this data to only the most predictive animal studies.

Moreover, the regulations go further and also require the pregnancy section of drug labels to include pharmacology information if the drug has a well-understood mechanism of action that may result in adverse developmental outcomes.²³⁷ The draft guidance for industry explains that examples to be included in this section involve drugs that interfere with DNA replication, induce cell death, or alter transmissions in major neurotransmitters.²³⁸ Because most drugs lack human data, pregnancy labels will be filled predominately with animal and pharmacology data. Though this data is relevant in constructing human clinical trials, as explained above, it is not reliably predictive of the

232. *Id.* at 72,084.

233. *Id.*

234. *Id.*

235. U.S. FOOD & DRUG ADMIN., PREGNANCY, LACTATION, AND REPRODUCTIVE POTENTIAL: LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS – CONTENT AND FORMAT, GUIDANCE FOR INDUSTRY 8 (2014) [hereinafter PREGNANCY, LACTATION, AND REPRODUCTIVE POTENTIAL], available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>.

236. See *supra* Part II.A for a discussion of the use of animal data on drug labels.

237. 79 Fed. Reg. at 72,101–02.

238. PREGNANCY, LACTATION, AND REPRODUCTIVE POTENTIAL, *supra* note 235, at 9.

human drug response. For this reason, it is unclear whether such information can form the basis of informed decision-making, or has any place on drug labels.

The regulations for animal data require the following information be displayed: “Types of studies, animal species, dose, duration and timing of exposure, study findings, presence or absence of maternal toxicity, and limitations of the data. Description of maternal and offspring findings must include dose-response and severity of adverse developmental outcomes.”²³⁹ Given that all of this information would need to be displayed about every animal study conducted, these labels will become large and complicated. The presence of a number of such studies might leave pregnant women who lack scientific training with a false impression even when the animal data is of a relatively high quality. When there are many low-quality animal studies on a label, pregnant women might not grasp the data’s comparative unreliability.

The FDA continues to promote the use of animal data on its labels despite an awareness of its shortcomings. For instance, in the new regulations the agency acknowledges the importance of human data: “[T]he positive and negative predictive values of animal studies for humans are often uncertain. In screening for drug-induced fetal effects, animal models can be misleading by suggesting associations that ultimately turn out to be false positive or false negative in humans.”²⁴⁰ The agency even understands the consequences of failing to generate this information as it stated:

Most health care providers are not able to translate animal reproductive toxicity data into an accurate assessment of human teratogenic risk. Thus, in the absence of human data, it is difficult for health care providers to adequately counsel patients about the risks of drug use in pregnancy. Without adequate counseling, women may decide to take steps to avoid becoming pregnant while on needed drug therapy, to forego needed drug therapy while pregnant, or to terminate pregnancies.²⁴¹

In an attempt to generate more human data, the agency endorses pregnancy exposure registries as a solution to the problem.²⁴² The regulations require pregnancy exposure registry information, if available, to be placed on drug labeling to encourage consumer involvement.²⁴³ As discussed above, however, post-market-approval studies generate much less reliable data than human clinical trials.²⁴⁴ In the final rule, the FDA acknowledges this fact. One

239. 79 Fed. Reg. at 72,101–02.

240. 73 Fed. Reg. 30,831, 30,841 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

241. *Id.*

242. 73 Fed. Reg. 30,839, 30,863–67; 79 Fed. Reg. 72,101.

243. 79 Fed. Reg. 72,101.

244. See Kennedy, Uhl & Kweder, *supra* note 131 (explaining the scientific limitations of pregnancy exposure registries and identifying them as best used as a hypothesis-generating tool or

commenter noted “sufficient data must be based on large-scale epidemiologic studies or clinical trials, and cannot be based on pregnancy registries or case reports/series requiring further evaluation.”²⁴⁵ The FDA responded that it “recognizes that because retrospective voluntary adverse event reporting may be biased and incomplete, spontaneous reports cannot rule in or out a causal relationship between drug exposure and clinical outcome.”²⁴⁶ The agency, however, ultimately concluded that pregnancy registries could provide valuable information. Though this post-approval data does have some value, the FDA generally only uses it to monitor risks, not to generate first-in-population data.²⁴⁷ The FDA’s requirement that the labeling promote these registries condones off-label drug consumption by pregnant women despite known risks.²⁴⁸ In this way, the FDA’s solution to the lack of information in pregnancy is inconsistent with its general practice.

C. Consequences of the FDA Pregnancy Labeling Regulations

Pregnancy labeling of drugs is very important; both women and doctors refer to it when deciding if they should consume or prescribe medications during pregnancy.²⁴⁹ The way that data is displayed, and whether it has a cautious tone, will impact decision-making. Current FDA regulations are inadequate. Even when human data exists and fails to demonstrate risk, the regulations encourage precaution and restraint.²⁵⁰ This restraint is encouraged despite the fact that over-caution with drug consumption can be harmful.²⁵¹ Finally, the risks to pregnant women themselves are not included anywhere in the labeling despite genuine risks for their safety.²⁵² This sends the message that the only legitimate factors in drug consumption are fetal risk and benefit.

The new regulations are an important improvement. Not only are they more descriptive and informative, but they also provide greater insight into the maternal and fetal risks associated with pregnant women’s avoiding and

to identify major risks); *see also* Junod, *supra* note 136, at 2 (“Although simple observation may provide a starting point for medical study, however, experience has shown that it is rarely efficient at advancing medical knowledge.”). The same article also noted the evolution of clinical trials to culminate in the double-blind, placebo controlled trail as the most reliable, gold-standard method of generating reliable data. *Id.*

245. 79 Fed. Reg. at 72,081.

246. *Id.* at 72,082.

247. *See* Kennedy, Uhl & Kweder, *supra* note 131.

248. *See supra* Part I.B for a discussion of the risks associated with pregnant women consuming medications without data on their safety or effectiveness.

249. 73 Fed. Reg. 30,831, 30,841 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

250. *See* Table One.

251. *See* Part I.B.

252. *See* Table One.

consuming needed medications.²⁵³ They remove any unnecessary blanket warnings to avoid drug consumption and include information about background risk.²⁵⁴ They fail, however, to address the main problem: a lack of data. The regulations encourage pregnancy exposure registries to generate human data, which are less informative than tests on human subjects.²⁵⁵ The agency also continues to include animal and pharmacologic data, even though this is not used for any other subpopulation and has unclear predictive value for humans.²⁵⁶ Pregnancy labeling is a unique FDA practice. Though providing access to data is extremely important, there should be a focus on access to reliable data. More access to unreliable data might not serve to help women make informed decisions.

III.

AN APPROACH TOWARD IMPROVING ACCESS TO DRUG RISK INFORMATION IN PREGNANT WOMEN

Protecting pregnant women from the risks of drug consumption will involve a lot of moving parts. First, it will involve altering the IRB regulations to ensure that IRBs stop effectively banning pregnant women from medical research. Because pregnant women are not more susceptible to coercion,²⁵⁷ they should be treated as other adults and allowed to participate in ethical medical research as defined by 45 C.F.R. § 46.111 (a)–(b). As discussed in greater depth below, 45 C.F.R. § 46.111(b) will ensure that the IRB accounts for the uniqueness of the fetal-woman relationship in a way that is specific to a given protocol.

Though removing Subpart B would make it less burdensome to get clinical trials involving pregnant women approved by IRBs, drug companies might still avoid clinical trials in pregnant women. If pharmaceutical companies are not forced to generate this information, and they do not expect to benefit financially from providing it, they will continue to avoid conducting these clinical trials despite the removal of regulatory hurdles. Thus, financial incentives should be developed to encourage drug companies to invest in this data production. This Part argues that providing pharmaceutical companies with a period of regulatory exclusivity if they conduct clinical trials in pregnant women is the best financial incentive to promote this needed research. This was successfully accomplished in the pediatric context. Finally, once these financial obstacles are removed and this data is generated, the FDA labeling guidelines should be altered to rely solely on human data, treating pregnant women as the agency treats other

253. 79 Fed. Reg. 72,064, 72,101–02 (proposed Dec. 4, 2014) (to be codified at 21 C.F.R. pt. 201).

254. *Id.* See Table One for the past regulations and the blanket warnings that were required.

255. *Id.*

256. *Id.*

257. For reference to the classification of pregnant women as a “vulnerable” group, see 45 C.F.R. § 46.111(a)(3). For a critical discussion of this classification, see Part I.C.

populations. In this scenario, the pregnancy labeling requirements would look more like the pediatric labeling requirements and foster informed decision-making for pregnant women.

A. Eliminate Subpart B and Encourage IRB Members to View Pregnant Women as Complex, Not Vulnerable

A critical step in any comprehensive reform would include amending the regulations on ethical human subjects research. Regulating research in pregnant women under the same framework used for children and prisoners is unnecessary and unjustified. Pregnant women are no more vulnerable than other adults to coercion.²⁵⁸ They are capable of weighing the costs and benefits to themselves and their fetuses in deciding whether to participate in research. While some people may be uncomfortable with the idea of pregnant women consuming drugs with unknown risk profiles, the alternative is to expose many more pregnant women to similar risks without the protections IRBs provide when they review and approve research protocols. The risks pregnant women endure in the clinical setting do not benefit society by providing scientific knowledge and, if they produce any data at all, it is much less reliable than data from clinical trials.²⁵⁹

Many bioethicists have argued that research on pregnant women needs to move from a presumption of exclusion to a presumption of inclusion.²⁶⁰ In this framework, IRBs would have to justify every decision to exclude pregnant women from clinical trials, whereas now, they feel they must justify every decision to include them.²⁶¹ This recommendation must be incorporated into IRB practice. A recent article in *Women's Health Issues* contains a further proposal on how to alter the IRB regulations.²⁶² The authors recommend reclassifying pregnant women as “complex” rather than “vulnerable,” and creating a special ethical framework to accompany the new title.²⁶³ This recommendation is helpful, but ultimately the authors could have gone further by simply rejecting Subpart B altogether. Though this may initially seem reckless, 45 C.F.R. § 46.111(b) would provide adequate protections that could recognize the uniqueness of the fetal-woman relationship. Section 46.111(b) lists five subpopulations: “children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.”²⁶⁴ Two of

258. See Schonfeld, *supra* note 49, at 204.

259. See Junod, *supra* note 136, at 2.

260. See, e.g., Mary C. Blehar, Catherine Spong, Christine Grady, Sara F. Goldkind, Leyla Sahin & Janine A. Clayton., *Enrolling Pregnant Women: Issues in Clinical Research*, 23 *WOMEN'S HEALTH ISSUES* e39, e42 (2013); *The Second Wave*, *supra* note 3; *Pregnancy and Clinical Research*, *supra* note 3; *Reframing the Framework*, *supra* note 3.

261. Blehar, Spong, Grady, Goldkind, Sahin & Clayton, *supra* note 260.

262. *Id.*

263. *Id.* at e41–42.

264. 45 C.F.R. § 46.111(b) (2013).

them (the mentally disabled, and economically or educationally disadvantaged) are not considered vulnerable enough to have a dedicated subpart. However, 45 C.F.R. § 46.111(b) requires IRBs to ensure that research involving the five listed populations provide “additional safeguards . . . to protect the rights and welfare of these subjects.”²⁶⁵ This protection would be provided even if a population does not have its own subpart. For instance, the mentally incapacitated do not have their own subpart, but IRBs are still aware of the complications of conducting research in this population and alter their review accordingly.²⁶⁶

Under this framework, Subpart B would be eliminated, but pregnant women would remain in 45 C.F.R. § 46.111(b), which would provide them and their fetuses with additional safeguards. This could help bring about the presumption toward inclusion and force researchers to justify their reasons for excluding pregnant women.²⁶⁷ This is a vital, and long overdue change: “[s]ince the NIH began to require inclusion of women, ethnic minorities, and children in research, pregnant women are the only population for which justification for exclusion does not need to be given.”²⁶⁸ Removing Subpart B and requiring IRBs to justify exclusion would go a long way toward changing the feasibility of conducting clinical trials in pregnant women.

Continuing to include pregnant women in the 45 C.F.R. § 46(b) regulations, however, would indicate that the presence of a fetus does alter certain considerations. But instead of allowing the IRB to automatically exclude the pregnant population, the board would have to debate whether allowing pregnant women in a particular research study was appropriate. IRB members could continue to reference the previous Subpart B regulations as a consideration when thinking of the ethical issues associated with pregnant women participating in research, but they would no longer be bound to them in each individual research protocol. For instance, IRBs might still require data in pregnant animals and non-pregnant women before approving a protocol in pregnant women, however the data demanded would need to be the least required to assure a minimum level of safety. Furthermore, if in an individual case, an IRB did not think both sets of data was necessary, it could only require one.

As the issue surrounding the IRB regulations has largely been one of unnecessarily conservative IRB interpretation of the regulations, eliminating Subpart B would need to be accompanied by IRB education. IRBs need to be instructed about the importance of including pregnant women in research, and why they need to grant approval when “additional safeguards have been included.”²⁶⁹ This model acknowledges the importance of the fetus without requiring that women’s health, which directly impacts the health of their fetuses, be jeopardized because of perceived fetal risk. This shift would also clarify that

265. *Id.*

266. GUIDEBOOK, *supra* note 19, at ch. 6 pt. D.

267. Blehar, Spong, Grady, Goldkind, Sahin & Clayton, *supra* note 260, at e41–42.

268. *Id.* at e42.

269. 45 C.F.R. § 46.111(b).

“in practice the notion of maternal-fetal conflict poses a false dichotomy” and that maternal and fetal health are in fact very hard to separate.²⁷⁰

B. Create Financial Incentives to Encourage the Generation of Drug-Safety Data

Reframing the IRB regulations is vital to permitting pregnant women to participate in clinical trials. Without incentives or requirements to produce this research, however, drug companies are unlikely to spend the time and resources to generate this information. There are a few possible methods to change this. First, Congress could permit the FDA to require this data. This would be the least expensive, and most effective way to generate this research given that the cost would be incurred solely by the pharmaceutical industry. Unfortunately, drug companies would likely vigorously oppose this regulatory shift due to its great cost potential. Given the power of the pharmaceutical lobby,²⁷¹ such a reform would likely be politically unfeasible. Second, Congress could set aside funds exclusively for researchers studying the effects of drugs in pregnant women.²⁷² This would require the government to find and set aside tax dollars to support such a program, which given the current financial crisis and how sequestration has effected NIH research grant funds, is also politically problematic.²⁷³ Finally, Congress could create incentives to produce this information—for instance, through the creation of periods of regulatory exclusivity, much like what was done in the pediatric context.²⁷⁴ The argument against this model is that it is expensive for drug consumers and creates a windfall for the pharmaceutical industry.²⁷⁵ This model, however, did produce a wealth of information regarding drug safety in children and is generally considered a success.

In the pediatric setting, after similar concerns about a lack of information, Congress amended the Food and Drug Modernization Act in 1997.²⁷⁶ This law provided a six-month period of market exclusivity for drugs that had undergone

270. Blehar, Spong, Grady, Goldkind, Sahin & Clayton, *supra* note 260, at e41–42.

271. See Paul Blumenthal, *Auction 2012: How Drug Companies Game Washington*, HUFFINGTON POST (Feb. 1, 2012, 12:56 PM), http://www.huffingtonpost.com/2012/02/01/auction-2012-drug-companies-lobby_n_1245543.html (“There are few industries with as much power in Washington as the pharmaceutical sector. Drug companies have spent \$2.3 billion on lobbying and \$183 million on campaign contributions since 1998, according to the Center for Responsive Politics.”).

272. See Greenwood, *supra* note 3, at 315.

273. *Fact Sheet: Impact of Sequestration on the National Institutes of Health*, NATL. INSTS. OF HEALTH (June 4, 2013), <http://www.nih.gov/news/health/jun2013/nih-03.htm>.

274. See Greenwood, *supra* note 3, at 310–11.

275. *Id.* at 314.

276. See Rebecca S. Eisenberg & John R. Thomas, *Patents and Regulatory Exclusivity in the USA*, in 2 *ENCYCLOPEDIA OF HEALTH ECONOMICS*, 443, 447 (Anthony J. Culyer ed., 2014).

pediatric clinical trials.²⁷⁷ This exclusivity was tacked on to whatever exclusivity the drug company already retained and did not require findings that the drug was safe in children.²⁷⁸ Regulatory exclusivity has similar benefits to the patent system, but is protected through the FDA as opposed to patent infringement litigation. If a drug company is entitled to this additional exclusivity, then the FDA will not approve another drug to share the market space until that additional six months has passed.²⁷⁹ This has yielded a “significant increase in available information about the effects of drugs in children.”²⁸⁰ Within a decade of the law’s enactment, over 300 pediatric studies had been conducted.²⁸¹ Moreover, “[w]hile there were only eleven pediatric labeling changes between 1990 and 1997, there were one hundred thirty between 1997 and 2007.”²⁸² The cost of this information for drug consumers was significant, however, in that it delayed the entry of cheaper generics by six months.²⁸³ In the six months of market exclusivity granted for pursuing research in children, drug companies stood to make large returns on investment.²⁸⁴

Kate Greenwood has examined whether this model would be appropriate in the pregnancy setting.²⁸⁵ She notes many criticisms of the pediatric exclusivity provision, determining that “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.”²⁸⁶ Instead, she concludes that a system of federally funded and mandated research would be ideal.²⁸⁷ Even if Greenwood’s proposal would be better for consumers, her solution is financially and politically impracticable in light of the current financial crisis and the unwillingness of Congress to support efforts to conduct research on pregnant women.²⁸⁸

Legislation providing regulatory exclusivity for conducting clinical trials in pregnant women—the most feasible option for generating important data in our current political climate—should be pursued. If Congress was concerned about

277. *Id.*

278. *Id.*

279. *Id.* at 448.

280. *Id.*

281. See Jennifer S. Li, Eric L. Eisenstein, Henry G. Grabowski, Elizabeth D. Reid, Barry Mangum, Kevin A. Schulman, John V. Goldsmith, M. Dianne Murphy, Robert M. Califf & Daniel K. Benjamin, Jr., *Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program*, 297 J. AM. MED. ASS’N 480, 480 (2007).

282. Greenwood, *supra* note 3, at 312.

283. *Id.* at 314.

284. *Id.* at 313–14.

285. *Id.* at 314.

286. *Id.*

287. *Id.* at 322.

288. See Li, Eisenstein, Grabowski, Reid, Mangum, Schulman, Goldsmith, Murphy, Califf & Benjamin, *supra* note 281.

the potential cost to consumers, it could legislate a shorter period of exclusivity. Additional months of exclusivity would create incentives for drug companies to generate this research, as they would stand to make tens of millions of dollars.²⁸⁹ It is additionally important to note that while consumers may be financially burdened by this system, they also stand to benefit from it. Without this information, pregnant women will continue to be under-informed about the risks of drug use and suffer health complications as a result.²⁹⁰ Six months of delayed generic entry may be a fair price to pay for such information, especially if it is the only practical option available at this time.

C. Amend the Labeling Regulations Again to Display Neutral Information on Maternal and Fetal Risks

Finally, once more data has been generated, the FDA should further alter its pregnancy labeling regulations. With risk data in pregnant women available, the new FDA labeling regulations represent an important step forward. However, once pregnancy risk data is produced, altering the standards for pregnancy labeling to reflect the standards for pediatric labeling will be the crucial, final step. Pediatric labeling is minimal.²⁹¹ It requires a “pediatric use” section when pediatric dosing differs from adult dosing; a description of human pediatric data if such data indicates safety or risks; a neutral statement that pediatric studies have not been conducted, if applicable, without drawing any conclusions one way or another; and an indication of pediatric risks in either the “warnings and precautions” or “contraindication” section.²⁹² Most importantly, animal data should be used minimally—only when reliable human data is unavailable and where the animal data is particularly predictive.²⁹³ Appropriate disclaimers about reliability should accompany animal data.

Displaying pregnancy data in this way would be more consistent with FDA practice. The FDA’s role is to require neutral information to be displayed on drug labeling so that people can make autonomous, well-informed decisions on drug consumption. Pregnant women are equally capable of evaluating risks and determining what is in their best interests. The FDA must simply present data, not attempt to bias decision-making one way or another. The only way to ensure this occurs is to treat the risks of medication in pregnant women consistently with other subpopulations.

289. If the median profit generation from six months of market exclusivity is \$140 million and the median cost of clinical trials is \$10 million, then the median three month market exclusivity should still yield around \$60 million. *See Greenwood, supra* note 3, at 314.

290. *See* Part I.B.

291. *See* 21 C.F.R. § 201.57(c)(9)(iv) (2014).

292. *Id.*

293. For instance, when “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,” there are reasons to doubt the predictability of the data in humans. *See Greenwood, supra* note 3, at 284.

Taken together, regulatory reform of IRB regulations, market incentives for generating data, and an amendment of FDA labeling requirements would greatly improve access to, and proper display of, information regarding maternal and fetal risk of drug consumption during pregnancy. Removing pregnant women from the category of vulnerable populations would reduce the burden of conducting research in pregnant women. Creating incentives for generating human data through market exclusivity would remove any financial barriers and encourage this data production. Finally, displaying this human data in a neutral manner, without relying on animal studies, would make pregnancy information more consistent with other risk subsections. These three changes would have a huge impact on pregnant women. It would improve decision-making and greatly reduce the risks inherent in drug consumption or drug avoidance.

CONCLUSION

Regulations that govern FDA labeling create an environment in which pregnant women are discouraged from taking needed medications due to potential risks to their fetuses. These precautions are based on a lack of human data. This data is missing, however, largely because of overly protective and paternalistic regulations that create a presumption against including pregnant women in medical research. The bioethics community has harshly criticized these regulations as paternalistic and dangerous to pregnant women. The best way to solve this problem is to generate human data and display neutral information in product labeling. This article has suggested three changes: (1) removing pregnant women from the classification as a vulnerable research population; (2) creating a system of market exclusivity to generate drug studies involving pregnant women; and (3) altering FDA labeling regulations to exclusively reflect this evidence. All three recommendations in tandem would greatly improve pregnant women's access to reliable information on drug risks and help them to make well-informed medical decisions.