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# The Desperate Need to Include Pregnant Women in Clinical Research: Proposed Recommendations to Increase Enrollment of Pregnant Women in Research

Julia Belton

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THE DESPERATE NEED TO INCLUDE PREGNANT WOMEN IN CLINICAL  
RESEARCH: PROPOSED RECOMMENDATIONS TO INCREASE ENROLLMENT OF  
PREGNANT WOMEN IN RESEARCH

Julia Belton

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## INTRODUCTION

The lack of human data available to make evidence-based decisions about medicine taken during pregnancy has heightened awareness that pregnant women should be included in biomedical research.<sup>1</sup> However, regulations, guidance, and the current clinical trial landscape reflect an exclusionary approach to research. This paper explores the lack of data available for pregnant women and healthcare practitioners to make informed decisions about the safety of medication taken during pregnancy and changes the federal government could make in an attempt to increase knowledge and data for medications taken during a pregnancy.

The CDC estimates that 133 million Americans, almost one out of every two adults, have at least one chronic illness.<sup>2</sup> Many pregnant women have medical conditions that require prescription medications, yet most drugs are approved without any clinical research on their safe use during pregnancy.<sup>3</sup> These untested medications may treat preexisting chronic conditions such as diabetes or seizures.<sup>4</sup> A study describing medication use during pregnancy showed that the overall use has increased during the past 30 years, and a majority of women took at least one prescription drug during pregnancy.<sup>5</sup> The failure to understand the risks and benefits of medication use during pregnancy can result in inadvertent exposure to the fetus, pregnancy termination, or

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<sup>1</sup> See *infra* notes 5–12, and accompanying text.

<sup>2</sup> *Chronic Diseases and Health Promotion*, CDC.GOV, <http://www.cdc.gov/chronicdisease/overview/index.htm> (last visited Mar. 11, 2014).

<sup>3</sup> *Pregnancy Research*, CDC.GOV, <http://www.cdc.gov/pregnancy/meds/research.html> (last visited Mar. 11, 2014).

<sup>4</sup> Pellavi Sharma, et al., *An Innovative Approach To Determine Fetal Risk*, 18 WOMEN'S HEALTH ISSUES, 226, 228 (2008).

<sup>5</sup> Allen Mitchell et al., *Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008*, 205 AM. J. OBSTETRICS & GYNECOLOGY 51.e1 (2011).

alternatively, discontinuation in medication that may cause maternal or fetal harm.<sup>6</sup>

However, there is reluctance to conduct clinical research in pregnant women because of ethical concerns. Pregnant women are a challenging population to conduct research because of concerns of potential adverse effects of medication exposure to the developing fetus.<sup>7</sup> For example, it would be unethical to randomize pregnant women to receive antidepressant drugs with unknown safety profiles.<sup>8</sup> Although there may be situations when exclusion of pregnant women from research is justified, because of ethical concerns, pregnant women are often reflexively excluded.<sup>9</sup>

A major concern for taking medication during pregnancy is the potential for fetal adverse effects, or that drug pharmacokinetics are “commonly altered in pregnancy, potentially affecting optimal dosing.”<sup>10</sup> Except for the few products developed to treat conditions unique to pregnancy, prescription drugs are not tested in pregnant women prior to their approval, resulting in no data from controlled clinical trials.<sup>11</sup> Risks and benefits for the mother and fetus must carefully be weighed before prescribing, yet is a challenge because of the scarcity of information available.<sup>12</sup>

Part I of this paper examines the historical background of women’s participation

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<sup>6</sup> Lydia E. Pace & Eleanor Bimla Schwarz, *Balancing act: safe and evidence-based prescribing for women of reproductive age*, 8 J. WOMEN’S HEALTH 415, 416 (2012).

<sup>7</sup> Meghan Coakley, et al., *Dialogues on Diversifying Clinical Trials: Successful Strategies for Engaging Women and Minorities in Clinical Trials*, 21 J. WOMEN’S HEALTH 713 (2012).

<sup>8</sup> Fabiano Santos et. al. *Quality Assessment of Clinical Practice Guidelines for the Prescription of Antidepressant Drugs During Pregnancy*, 7 CURRENT CLINICAL PHARMACOLOGY 7, 8 (2012).

<sup>9</sup> Kristine Shields & Anne Drapkin Lyerly, *Exclusion of Pregnant Women From Industry-Sponsored Clinical Trials*, 122 AM. C. OBSTETRICIANS & GYNECOLOGISTS 1077 (2013).

<sup>10</sup> Simon Thomas & Laura Yates, *Prescribing without evidence – pregnancy*, 74 BRIT. J. CLINICAL PHARMACOLOGY 691, 692 (2012).

<sup>11</sup> Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling, 73 Fed. Reg. 30831-01, 30841 (proposed May 29, 2008) (to be codified at 21 C.F.R. pt. 201).

<sup>12</sup> Thomas & Yates, *supra* note 10 at 691; See also Paul Doering, et al., *Review of pregnancy labeling of prescription drugs: Is the current system adequate to inform of risks?* AM. J. OBSTETRICS & GYNECOLOGY 333, 335 (2002).

in clinical trials. Part II reviews the lack of evidence-based data for medication taken during pregnancy. Part III assesses current regulations and guidance, and explains why they are unsatisfactory. Part IV evaluates the current landscape of clinical research in pregnant women in order to demonstrate the consequences of the lack of scientific data. Part V recommends changes to federal regulations, or in the alternative, an incentive-based program to increase the enrollment of pregnant women in clinical research.

#### I. HISTORICAL EVOLUTION OF WOMEN AND CLINICAL RESEARCH – FROM COMPLETE EXCLUSION TO AN EXCLUSIONARY APPROACH

##### *A. History of Women As Research Subjects Before Guidelines & Congressional Response to Exclude Women as Research Subjects*

During the early nineteenth century, clinical trials depended upon the experimentation of surgical procedures and methods on female American slaves, followed by institutionalized populations and prisoners in the twentieth century.<sup>13</sup> Following the exposure of German brutalities during World War II, the Nuremberg Code created the first internationally recognized standards for human research.<sup>14</sup>

In 1953, the Clinical Center at the National Institutes of Health established a policy for the protection of human subjects.<sup>15</sup> For NIH clinical research, this policy required informed consent of all subjects, and review and approval of research.<sup>16</sup>

Following the NIH policies, Congress began to issue a number of laws and standards for the protection of human subjects in research. In 1962, Congress passed the Drug Amendments, which required that researchers testing investigational new drugs

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<sup>13</sup> See Ruth B. Merkatz & Suzanne W. Junod, *Historical Background of Changes in FDA Policy on the Study and Evaluation of Drugs in Women*, 69 ACAD. MED. 703 (1994).

<sup>14</sup> *Id.*

<sup>15</sup> Joseph L. Breault, *Protecting Human Research Subjects: The Past Defines the Future*, 6 OCHSNER J. 15, 20 (2006).

<sup>16</sup> *Id.*

now had to obtain consent from research subjects.<sup>17</sup>

In 1974, Congress passed the National Research Act that mandated approval by an IRB of human subjects research at any institution receiving DHHS funding.<sup>18</sup> This extended additional protections to research subjects of biomedical research, development, and related activities involving, among other groups, fetuses, and pregnant women.<sup>19</sup>

However, in 1977 the FDA issued a guideline for drug development recommending that women of childbearing potential be excluded from clinical drug trials.<sup>20</sup> This exclusion was applied broadly to any “premenopausal female being capable of becoming pregnant.”<sup>21</sup> Although this exclusion was applicable to only women of childbearing potential from early phases of drug trials, investigators and IRBs applied this to all phases of drug trials.<sup>22</sup>

### *B. Shift Away from Excluding Women in Clinical Research*

In 1986 NIH policy was changed to encourage the inclusion of women in research to require a justification for exclusion of women as well as evaluate gender differences in the future.<sup>23, 24</sup> In 1990, the Women’s Health Equity Act was passed, and the Office for

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<sup>17</sup> *Id.*

<sup>18</sup> *Id.*

<sup>19</sup> Protection of Human Subjects, 45 C.F.R. § 46 (1975).

<sup>20</sup> U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., GENERAL CONSIDERATIONS FOR THE CLINICAL EVALUATION OF DRUGS 7 (1977).

<sup>21</sup> *Id.* See also Marianne Prout & Susan Fish, *Participation of women in clinical drug trials of drug therapies: a context for the controversies*, 3 MEDSCAPE GEN. MED. 4 (2001) (noting that the exclusion from drug trials also included all women using contraception, women with male partners, and single women; and concluding that changes were prompted from public and political attention by the thalidomide tragedy which resulted in over 10,000 children with birth defects worldwide to focus on drug approval processes).

<sup>22</sup> Janet E. Shepard, *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies* 272 JAMA 1467 (1994).

<sup>23</sup> U.S. DEP’T OF HEALTH & HUMAN SERVICES, PUBLIC HEALTH SERVICE, NATIONAL INSTITUTES OF HEALTH, OFFICE OF RESEARCH ON WOMEN’S HEALTH, ENROLLING PREGNANT WOMEN: ISSUES IN CLINICAL RESEARCH (2011), available at <http://orwh.od.nih.gov/resources/policyreports/pdf/ORWH-EPW-Report-2010.pdf> (noting that the historical research tragedies were due to the problem that research had not been conducted to validate the use of the product).

<sup>24</sup> See *Maternal-Fetal Medicine Units (MFMU) Network*, NICHD.NIH.GOV, <http://www.nichd.nih.gov/research/supported/Pages/mfmu.aspx> (last visited May 6, 2014) (also in 1986,

Research on Women's Health was established.<sup>25</sup> The NIH Revitalization Act of 1993 required that women must be included in all NIH-funded clinical research, unless a clear and compelling rationale and justification established that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research.<sup>26</sup> Specifically, this policy states that women of childbearing potential should not be routinely excluded from participation in clinical research.<sup>27</sup> The Act does not address research in pregnant women.

In 1993, the FDA lifted the 1977 guideline excluding women of childbearing potential.<sup>28</sup> This notice explained that subgroup-specific differences in response can arise because of variations in a drug's pharmacokinetics or pharmacodynamics.<sup>29</sup> The FDA acknowledged that the removal of the prohibition on participation of women of childbearing potential was consistent with congressional efforts to prevent unwarranted discrimination against women.<sup>30</sup> While these guidelines removed the prohibition of women in clinical trials, the FDA did not require female participation, nor did it address potential benefits of including pregnant women. A lack of direction in combination with advice to avoid pregnancy highlights the ethical dilemma of enrollment.<sup>31</sup> The Food and Drug Administration Modernization Act of 1997 mandated the review and development

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the NIH Child Health and Human Development established the Maternal-Fetal Medicine Units Network to response to the need for well-designed clinical trials within maternal-fetal medicine, specifically preterm birth, with a focus to evaluate interventions for efficacy, safety and cost-effectiveness).

<sup>25</sup> *Id.*

<sup>26</sup> See *NIH Policy and Guidelines on The Inclusion of Women and Minorities as Subjects in Clinical Research*, NIH.GOV, [http://grants1.nih.gov/grants/funding/women\\_min/guidelines\\_amended\\_10\\_2001.htm](http://grants1.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm) (last visited Mar. 11, 2014).

<sup>27</sup> *Id.*

<sup>28</sup> Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs, 58 Fed. Reg. 39,406, 39,409–11 (July 22, 1993) [hereinafter the 1993 FDA GUIDELINE].

<sup>29</sup> *Id.*

<sup>30</sup> *Id.*

<sup>31</sup> See 1993 FDA GUIDELINE, 58 Fed. Reg. 39,406 (the notice stated that precautions against becoming pregnant and exposing a fetus should be taken by women participating in clinical trials).

of guidance on the inclusion of women in clinical trials.<sup>32</sup>

In 1998, Congress passed a final rule that required New Drug Applications (NDAs) to present effectiveness and safety data for important demographic subgroups, specifically gender.<sup>33</sup> This rule also required sponsors to tabulate in their annual reports the numbers of subjects enrolled to date in clinical studies for drug and biological products according to age group, gender, and race in Investigational New Drugs (INDs).<sup>34</sup>

In 2014, the CDC launched an initiative, *Treating for Two: Safer Medication Use in Pregnancy*, to improve the quality of data and information on medication use during pregnancy.<sup>35</sup> The initiative seeks to expand medication safety research, evaluate evidence, and educate women and healthcare providers.<sup>36</sup>

## II. LACK OF EVIDENCE-BASED DATA FOR MEDICATION TAKEN DURING PREGNANCY IS A GRAVE ISSUE

Pregnant women need safe and effective treatment options, but are left with a severe lack of scientific data to support which option may be best during their pregnancy due to legal and ethical concerns. Pregnant women are severely underrepresented in the clinical research process, with the environment today as contrary to the core of social

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<sup>32</sup>See *Participation of Females in Clinical Trials and Gender Analysis of Data in Biologic Product Applications*, FDA.GOV, <http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/InvestigationalNewDrugINDorDeviceExemptionIDEDevelopment/ucm094300.htm> (last visited May 6, 2014) (explaining that the OWH research project examined the extent to which females have been included in clinical trials for biological products and to what extent the data from these studies have been analyzed and presented with respect to gender. The FDA formed the “FDAMA women and minorities working group” with representatives from the agency and the NIH to implement the section of the Act mandating the review and development of guidance, as appropriate, on the inclusion of women in clinical trials).

<sup>33</sup> Investigational New Drug Applications and New Drug Applications, 63 Fed. Reg. 6854-02 (Feb. 11, 1998) (to be codified at 21 C.F.R. pt. 312, 314).

<sup>34</sup> *Id.*

<sup>35</sup> *Medications and Pregnancy*, CDC.GOV, <http://www.cdc.gov/pregnancy/meds/> (last visited Apr. 18, 2014).

<sup>36</sup> *Treating for Two*, CDC.GOV, <http://www.cdc.gov/pregnancy/meds/treatingfortwo/facts.html> (last visited Apr. 18, 2014).

justice, where you treat others as dignified beings deserving of equal moral concern and to view others as independent sources of moral worth and dignity.<sup>37</sup> This is not the standard adhered to because pregnant women are not afforded the same attention and rigorous research as other populations.<sup>38</sup>

The FDA Office of Women's Health (OWH) advocates for the participation of women in clinical trials to better understand the biologic basis for sex differences because research has shown that sex as a variable contributes to differences in the safety and efficacy of drugs, biologics, and devices.<sup>39</sup> Data show that women experience more adverse drug reactions than men, and these reactions tend to be severe.<sup>40</sup> The 2001 GAO report found that of ten prescription drugs taken off the market by the FDA due to adverse events, eight were associated with greater health risks in women than men.<sup>41</sup>

In the past, most products approved by the FDA were studied exclusively in men in order to obtain FDA approval.<sup>42</sup> Pharmacological response may differ between men and women, with an increase of identification of sex-gender pharmacodynamic differences at a molecular level, however, these differences are understudied in women.<sup>43</sup> For example, in 2013 the FDA cut the recommended dose of zolpidem in half for women,

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<sup>37</sup> Mary Foulkes, et al., *Clinical Research Enrolling Pregnant Women: A Workshop Summary*, 20 J. WOMEN'S HEALTH 1429, 1432 (2011).

<sup>38</sup> *Id.*

<sup>39</sup> *Understanding Sex Differences*, FDA.GOV, <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm131182.htm> (last visited Apr. 18, 2014).

<sup>40</sup> Donald Mattison & Anne Zajicek, *Gaps in Knowledge in Treating Pregnant Women*, 3 GENDER MED. 169, 172 (2006).

<sup>41</sup> *Id.*

<sup>42</sup> *Inside Clinical Trials: Testing Medical Products in People*, FDA.GOV, <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143531.htm> (last visited Apr. 18, 2014).

<sup>43</sup> Flavia Franconi & Ilaria Campesi, *Pharmacogenomics, Pharmacokinetics & Pharmacodynamics: Interaction With Biological Differences Between Men And Women*, 171 BRIT. J. PHARMACOLOGY 580 (2014).

making this the only prescription in the U.S. with a different suggested dose by gender.<sup>44</sup>

Pregnancy further affects the ability of drug distribution, absorption, metabolism, and elimination.<sup>45</sup> Changes in the body's physiology during pregnancy may require the healthcare practitioner to increase or decrease a dose.<sup>46</sup> Specifically, pregnancy places different demands on the mother's circulatory system because the uterus and placenta require additional blood, increasing plasma volume faster than the blood cells increase.<sup>47</sup> This increase of blood volume requires extra work from the heart and kidneys, leaving a possibility that the drug may be excreted through a pregnant woman's kidneys faster than normal.<sup>48</sup> These changes also depend on the stage of pregnancy, so there may be clinically important changes in drug concentrations between various trimesters of pregnancy.<sup>49</sup>

A healthcare practitioner must blindly alter dosage for a pregnant woman because research was not conducted in this population. A 2011 study of all medications approved by the FDA from 1980 to 2010 found that 91% of the medications approved for use by adults did not have sufficient data for the use and risks of medication taken during pregnancy.<sup>50</sup> With the well known fact that the human body responds differently during pregnancy, it is unacceptable that this population is underrepresented in clinical research.

The largest study conducted on drug use during pregnancy is a 2004 retrospective study that evaluated the experience of pregnant women, and concluded that 64% of

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<sup>44</sup> Lesley Stahl, *Sex matters: Drugs can affect sexes differently*, CBS NEWS (Feb. 9, 2014), available at <http://www.cbsnews.com/news/sex-matters-drugs-can-affect-sexes-differently/>.

<sup>45</sup> Mattison & Zajicek, *supra* note 40.

<sup>46</sup> Michelle Meadows, *Pregnancy and the Drug Dilemma*, 35 FDA CONSUMER 16, 18 (2001).

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

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

<sup>49</sup> Thomas & Yates, *supra* note 10 at 693.

<sup>50</sup> MP Adam et al., *Evolving knowledge of the teratogenicity of medications in human pregnancy*, 157 AM. J. MED. GENET. 175 (2011).

pregnant women took a prescription drug before delivery.<sup>51</sup> Researchers also concluded “approximately one half of all pregnant women are prescribed drugs for which there is no evidence of safety during pregnancy in humans or for which there is evidence of fetal risk in animals or humans.”<sup>52</sup> An additional complication is that studies performed in animals are of limited value because adverse events may be species specific.<sup>53</sup> This further demonstrates the need to change the way research is conducted in order to gather data for prescription medications that are taken during pregnancy. A 2010 study showed that over the last three decades, first trimester use of prescription medicine increased by more than 60%, and the use of four or more medications more than tripled.<sup>54</sup> This study suggests there is also an increase of practitioners prescribing medications in addition to taking medication during pregnancy without pharmacokinetic data.

### III. CURRENT REGULATIONS AND GUIDANCE

DHHS regulations governing the protection of human subjects in research contain five subparts. Subpart A is the basic set of protections for all human subjects of research conducted or supported by HHS; this subpart is known as the Common Rule, because it has been adopted in identical form by 15 federal departments and agencies. The DHHS regulations also contains subparts B, C and D, which provide added protections for specific vulnerable groups of subjects, including pregnant women, prisoners and children, and subpart E, which governs IRB registration.<sup>55</sup>

The FDA is a DHHS agency that regulates clinical investigations of drugs,

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<sup>51</sup> Susan E. Andrade et al., *Prescription drug use in pregnancy*, 191 AM. J. OBSTETRICS & GYNECOLOGY 398 (2004).

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

<sup>53</sup> Thomas & Yates, *supra* note 10 at 692.

<sup>54</sup> Mitchell et al., *supra* note 5.

<sup>55</sup> *Regulations*, HHS.GOV, <http://www.hhs.gov/ohrp/humansubjects/index.html> (last visited May 6, 2014).

biological products and medical devices and has adopted and codified subparts A and D as FDA human subject protection regulations.<sup>56</sup> The FDA has not adopted regulations outlining special protections for pregnant women, fetuses or prisoners.<sup>57</sup>

*A. DHHS 45 C.F.R. Subpart B: Protection of Human Subjects*

Under subpart B, pregnant women may participate in research:<sup>58</sup>

- a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals and clinical studies, have been conducted and provide data for assessing potential risks to pregnant women;
- b. The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or fetus; or, if there is no prospect of benefit, the risk to the fetus is not greater than minimal;
- c. Any risk is the least possible for achieving the objectives of the research;
- d. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when the risk to the fetus is not greater than minimal, and her consent is properly obtained;
- e. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is properly obtained, except if the father is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
- f. Each individual providing consent here is fully informed regarding the reasonably foreseeable impact of the research on the fetus;
- g. Pregnant children must assent and obtain permission in accord with subpart D;
- h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
- i. Individuals engaged in the research will have no part in any decisions as to timing, method, or procedures used to terminate a pregnancy.
- j. Individuals engaged in research will have no part in determining viability.

The aforementioned regulations provide IRBs ten requirements for selecting pregnant women in clinical research. First, the regulations require a prerequisite to

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

<sup>57</sup> *Comparison of FDA and HHS Human Subject Protection Regulations*, FDA.GOV, <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/educationalmaterials/ucm112910.htm> (last visited May 6, 2014).

<sup>58</sup> 45 C.F.R. § 46.204.

research to conduct studies on non-pregnant women first. This condition is that preclinical studies must be conducted to provide data for an assessment of potential risks to pregnant women and fetuses. A concern is that a precondition of preclinical studies on non-pregnant women is that pregnant women are neglected or excluded from research. This requirement is to ensure that safety trials are ethical and do not expose the fetus to potential adverse harms. The Department agreed and noted that preclinical and clinical studies are required only when scientifically appropriate.<sup>59</sup>

Second, terminology in the regulations requires IRBs to determine the meaning of minimal risk and direct benefit. The regulations require that if there is no prospect of benefit from the trial, the risk to the fetus must not be greater than minimal. This means that the risk to the fetus is the least possible risk for achieving research objectives and any greater risk must be a direct benefit to the fetus or woman. However, there is a great problem amongst IRBs in determining the meaning of this phrase because “no more than minimal risk is extremely vague and interpreted by different IRBs in radically different ways.”<sup>60</sup> Additionally, IRBs are also left to determine the meaning of direct benefit, and whether there is a high probability of direct benefit, or if the probability is even relevant.

Subpart B grants IRBs the opportunity and the authority to ensure the adequacy of informed consent and protections by imposing additional requirements and monitoring the research or consent process.<sup>61</sup> The Department recognizes and encourages paternal involvement in decisions affecting the pregnant woman and fetus prior to delivery,

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<sup>59</sup> Protection of Human Research Subjects, 66 Fed. Reg. 3878-01, 3880 (Jan. 17, 2001) (to be codified at 45 C.F.R. pt. 46).

<sup>60</sup> *Regulatory Fixes And Clarification Needed For Involving Pregnant Women In Clinical Trials*, 18 NO. 5 GUIDE TO GOOD CLINICAL PRACTICE NEWSL. 10 (Feb. 2011).

<sup>61</sup> Protection of Human Research Subjects, 66 Fed. Reg. 3878-01 at 3880.

although there is a concern that the paternal consent is a barrier.<sup>62</sup> However, the regulations note that consent is not needed if the father is unavailable. Ultimately, the Department concluded that the decision-making authority for research participation of the pregnant woman or fetus prior to delivery should rest with the pregnant woman.<sup>63</sup>

### *B. FDA and the Enrollment of Pregnant Women in Clinical Trials*

The DHHS Protection of Human Subjects Regulations categorizes pregnant women as a vulnerable population and contains rules and guidance for research with pregnant women. While DHHS has special subparts relating to research for vulnerable populations, such as prisoners, and pregnant women, the FDA does not have comparable provisions for these populations.<sup>64</sup>

#### 1. FDA Tools to Ensure Demographic Data Analysis

In 1998, the FDA amended its regulations to require effectiveness and safety data for demographic subgroups, specifically gender, age and racial subgroups.<sup>65</sup> Therefore, the FDA is permitted to place a clinical hold on one or more studies under an IND if a sponsor proposes to exclude gender from participation in an investigation only because of risk or potential risk from the use of an investigational drug.<sup>66</sup> Furthermore, in 2007, the FDA required that prescription drug products must contain specific information about use in specific populations in the contents of drug labeling.<sup>67</sup> In a 2013 FDA report, a working group found that the FDA's internal policies, procedures and regulations facilitate the assessment of demographic subgroup information included in marketing

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

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

<sup>64</sup> *Comparison of FDA and HHS Human Subject Protection Regulations*, FDA.GOV, <http://www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/educationalmaterials/ucm112910.htm> (last visited May 6, 2014).

<sup>65</sup> See 21 CFR §§ 312, 314.

<sup>66</sup> 21 C.F.R. § 312.42.

<sup>67</sup> 21 C.F.R. § 201.56(7).

applications.<sup>68</sup> The FDA can communicate demographic information to the public after marketing approval through a variety of mechanisms, including product labeling, publicly posted clinical reviews, consumer updates, safety alerts, and label changes.<sup>69</sup>

While the FDA shifted their approach from excluding women in research to allowing women, the agency does not actively require or regulate research in pregnant women. The agency requires IND applications to include reports by sex; however the breakdown in this data is only male and female. The FDA fails to make an affirmative requirement to collect data on any pregnant woman involved in a clinical trial.

Additionally, the FDA issued draft guidance for a basic framework for designing and conducting clinical studies in pregnant women, 2004 *Guidance for Industry Pharmacokinetics in Pregnancy - Study Design, Data Analysis, and Impact on Dosing and Labeling*. The draft guidance provides recommendations to sponsors on how to assess the influence of pregnancy on the pharmacokinetics and the pharmacodynamics of drugs, as well as recommendations for investigators and researchers about issues to consider when designing and conducting PK studies in pregnant women.<sup>70</sup> The guidance adopts 45 C.F.R. § 46.204, stating that

Pregnant women may be involved in PK studies if the following conditions are met: preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risk to pregnant women and fetuses; and the risk to the fetus is not greater than minimal and the purpose of the research is the development of important

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<sup>68</sup> U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., *Collection, Analysis, and Availability of Demographic Subgroup Data for FDA-Approved Medical Products* (2013) available at <http://www.fda.gov/downloads/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcaact/significantamendmentstotheact/fdasia/ucm365544.pdf>.

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

<sup>70</sup> CENTER FOR DRUG EVALUATION & RES., U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: PHARMACOKINETICS IN PREGNANCY –STUDY DESIGN, DATA ANALYSIS, AND IMPACT ON DOSING AND LABELING (Oct. 29, 2004) [hereinafter 2004 FDA DRAFT GUIDANCE].

biomedical knowledge which cannot be obtained by any other means.<sup>71</sup>

The FDA acknowledges that the definition of minimal risk is broad and states that “fetal risk is considered minimal when the estimated risk to the fetus is no more than that from established procedures routinely used in an uncomplicated pregnancy or in a pregnancy with complications comparable to those being studied.”<sup>72</sup> The guidance anticipates that most of the studies in pregnant women will occur postmarketing from pregnant women who have already been prescribed the drug.<sup>73</sup>

This draft guidance does not encourage or incentivize industry or researchers to actively enroll pregnant women in studies. Clear agency guidance with affirmative actions items, such as the mandatory collection of postmarketing data or an active approach to recruitment, would enable the FDA to increase enrollment.

## 2. FDA Tools to Collect Data on Medications Taken During Pregnancy

The FDA published pregnancy exposure registry guidelines in 2002 and 2005, to encourage the collection of and to facilitate the analysis and interpretation of data regarding medication exposure during pregnancy.<sup>74</sup> These pregnancy exposure registries are a prospective observational study that examines fetal risk from medication exposure during pregnancy in which the enrollment criteria includes pregnant women already taking the medication where fetal outcomes have not yet been ascertained.<sup>75</sup>

When drug safety data is collected after a drug is licensed, problems may arise, such as the “lack of information about confounding factors, maternal adherence to

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<sup>71</sup> *Id.*

<sup>72</sup> *Id.*

<sup>73</sup> *Id.*

<sup>74</sup> See Sharma *supra*, note 4 at 228 (discussing the 2002 *Guidance for Industry: Establishing Pregnancy Exposure Registries* and the 2005 *Reviewer Guidance: Evaluating the Risks of Drug Exposure in Human Pregnancies*).

<sup>75</sup> *Id.*

prescribed medication, use of over-the-counter medicines...and difficulty in evaluating longer term effects.”<sup>76</sup> The FDA has not made pregnancy exposure registries mandatory for manufacturers to track data, but left this responsibility to the pregnant women taking the drug.<sup>77</sup> The agency explicitly states “since drug companies can’t test medicine on pregnant women, they may have little or no information about how these medicines could affect a woman or her fetus. Pregnancy registries are the best way to learn and to help women decide about taking medicines.”<sup>78</sup> The FDA had the opportunity to require industry to take a proactive approach to this research but failed to make this a requirement.

### *C. Non-binding Guidance Includes Pregnant Women in Clinical Research*

International and professional committees provide clearer guidance to include pregnant women in research. There is an opportunity to shift the paradigm from excluding pregnant women in clinical research to a presumption that pregnant women are eligible for relevant research.

The Council for International Organizations of Medical Science guidelines, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, relate mainly to ethical justification and scientific validity of research.<sup>79</sup> However, there is an explicit provision for pregnant women as research participants, which states

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<sup>76</sup> Thomas & Yates, *supra* note 10.

<sup>77</sup> See *How To Sign Up for a Pregnancy Exposure Registry*, FDA.GOV, <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm252397.htm> (last visited May 6, 2014). The FDA does not run pregnancy exposure registries and states the drug company that makes the medicine is usually in charge of the pregnancy registry. There is a list of medications available with a telephone number and link to connect the pregnant woman to the company in charge of the registry.

<sup>78</sup> *Id.*

<sup>79</sup> Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Geneva, 2002, at 74, available at ([http://www.cioms.ch/publications/layout\\_guide2002.pdf](http://www.cioms.ch/publications/layout_guide2002.pdf)) (last visited May 6, 2014) (CIOMS is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO).

Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility. Research in this population should be performed only if it is relevant to the particular health needs of a pregnant woman or her fetus, or to the health needs of pregnant women in general, and, when appropriate, if it is supported by reliable evidence from animal experiments, particularly as to risks of teratogenicity and mutagenicity.<sup>80</sup>

CIOMS justification of research involving pregnant women recognizes that it is complicated by the fact that it may present risks and potential benefits to two beings, the woman and the fetus, as well as to the person the fetus is destined to become.<sup>81</sup> The commentary states that special safeguards should be established to prevent undue inducement to pregnant women to participate in research in which interventions hold out the prospect of direct benefit to the fetus.<sup>82</sup> Finally, the commentary states that investigators should include in protocols on research on pregnant women a plan for monitoring the outcome of the pregnancy with regard to both the health of the woman and the short-term and long-term health of the child.<sup>83</sup> This guidance is clear in stating that pregnant women should be presumed eligible for participation in clinical research. A presumption of eligibility will deter the fear of the overbroad presumption of ineligibility.

A 2005 guideline from the European Medicines Agency, *Guideline on the Exposure to Medicinal Products During Pregnancy*, proposed active surveillance for the collection of post-authorization data in pregnancy.<sup>84</sup>

The American Congress of Obstetricians and Gynecologists issued a 2007

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

<sup>81</sup> *Id.*

<sup>82</sup> *Id.*

<sup>83</sup> *Id.*

<sup>84</sup> See Ruth Macklin, *Enrolling Pregnant Women In Biomedical Research*, 375 LANCET 632, 635 (2010) (noting that the guideline is applicable to newly marketed drugs and recommends a similar plan for older drugs lacking data).

Committee Opinion designed to provide reasonable guidelines for research involving women.<sup>85</sup> This opinion affirmatively states:

All women should be presumed to be eligible for participation in clinical studies. The potential for pregnancy should not automatically exclude a woman from participating in a clinical study, although the use of contraception may be required for participation. Inclusion of women in clinical studies is necessary for valid inferences about health and disease in women. The generalization to women of results from trials conducted in men may yield erroneous conclusions that fail to account for the biologic differences between men and women.<sup>86</sup>

ACOG's Committee on Ethics affirms both the need for women to serve as participants in research and the obligation for researchers, IRBs, and others reviewing clinical research to evaluate the potential effect of proposed research on women of childbearing potential, pregnant women, and the developing fetus.<sup>87</sup>

ACOG explicitly states that pregnancy should not automatically exclude a woman from participating in a study. However, as Part IV of this paper examines, most studies categorize pregnant women as part of the exclusionary criteria. ACOG's non-binding guidance recognizes the need to include women in studies but falls short of the presumption of eligibility for pregnant women to participate.

#### IV. TODAY'S ENVIRONMENT: BURDENS TO OVERCOME TO INCREASE ENROLLMENT OF PREGNANT WOMEN IN CLINICAL RESEARCH

The current clinical trial landscape does not demonstrate an inclusionary approach of pregnant women in clinical research. Despite the need to include pregnant women in drug trials, there is not a big push to enroll this population.<sup>88</sup> For example, only one drug, Makena, has been approved by the FDA for pregnancy indications in the past five

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<sup>85</sup> *Research Involving Women*, ACOG Committee Opinion No. 377. AM. C. OBSTETRICIANS & GYNECOLOGISTS (2007).

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

<sup>87</sup> *Id.*

<sup>88</sup> S Endicott & DM Haas, *The current state of therapeutic drug trials in pregnancy*, 92 CLINICAL PHARMACOLOGY & THERAPEUTICS 149, 150 (2012).

years.<sup>89</sup>

*A. Clinical Trials Do Not Actively Recruit Pregnant Women*

Using the NIH database for clinical trials, an analysis of Phase I, II and III studies for both industry and NIH or government funded including “pregnant” supports the gross underrepresentation of pregnant women in research.<sup>90</sup> Out of the 166,199 studies registered with ClinicalTrials.gov, there are 1,686 studies that include the term “pregnant.”<sup>91</sup> For trials sponsored by the NIH or other government funding, there are currently 71 studies in Phase I that include the term “pregnant,” 65 studies in Phase II, and 97 studies in Phase III.<sup>92</sup> For trials sponsored by industry, there are currently 9 studies in Phase I that include the term “pregnant,” 14 studies in Phase II, and 29 studies in Phase III.<sup>93</sup> However, these numbers overstate studies including pregnant women because the search returned studies in which “pregnant” was listed as an exclusion criteria. The few drug and biologic studies actively recruiting pregnant women were for HIV, influenza, malaria or a pregnancy related conditions.

According to this analysis using the NIH database, only two trials from NIH sponsors actively recruited pregnant women for a condition other than HIV, influenza, malaria or pregnancy related condition. The NIH or government funded studies yielded only two trials of interest. A Phase I vaccine trial was conducted in 48 pregnant women and 32 non-pregnant women to look at the safety and immunogenicity of a combination

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<sup>89</sup> *Id* at 149.

<sup>90</sup> Search for Studies, CLINICALTRIALS.GOV, <http://clinicaltrials.gov> (follow “advanced search” hyperlink; then search term “pregnant,” select study type “interventional studies,” select Phase “1” “2” and “3,” then follow “search” hyperlink) [hereinafter CLINICALTRIALS.GOV DATABASE SEARCH].

<sup>91</sup> *Id*.

<sup>92</sup> See CLINICALTRIALS.GOV DATABASE SEARCH, *supra* note 90 (follow search but select funder type “NIH,” “other US agency” and “all others;” then follow “search” hyperlink).

<sup>93</sup> See CLINICALTRIALS.GOV DATABASE SEARCH, *supra* note 90 (follow search but select funder type “industry;” then follow “search” hyperlink).

vaccine.<sup>94</sup> A Phase III trial for diabetic pregnant women actively recruited pregnant women with insulin-resistant diabetes mellitus, yet excluded pregnant women with type-I diabetes.<sup>95</sup> Noticeably absent were studies involving depression, asthma or hypertension.

The second interesting finding from the NIH database is that, out of the 52 studies containing the term “pregnant” in industry sponsored studies, zero studies actively recruited pregnant women for a condition other than HIV, influenza, malaria, or pregnancy related condition.<sup>96</sup> Pfizer and Cedars-Sinai Medical Center terminated a study, which recruited both men and women for the treatment of anxiety disorder.<sup>97</sup> While this study excluded pregnant women, the study required “partners of male participants who become pregnant during the course of the study to participate in order to collect safety information and understand the effects, if any, that the investigational drug may have on her pregnancy or the fetus.”<sup>98</sup> Here, industry is excluding pregnant women from studies and failed to actively recruit pregnant women for chronic condition research.

A 2012 report found that in the past two years, 264 drug trials have been registered and or performed specifically in pregnant women.<sup>99</sup> This report analyzed the ClinicalTrials.gov database with the keyword “pregnancy” and searched the abstracts from annual meetings from five organizations.<sup>100</sup> However, the report found that it was impossible to determine how many of the trials were being performed on investigational drugs or where the funding came from because of inconsistent data between the website

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<sup>94</sup> *Pertussis Vaccine in Healthy Pregnant Women*, CLINICALTRIALS.GOV, <http://clinicaltrials.gov/show/NCT00707148> (last visited May 6, 2014).

<sup>95</sup> *Metformin as Adjuvant to Insulin Therapy in Insulin-resistant Diabetes Mellitus With Pregnancy*, CLINICALTRIALS.GOV, <http://clinicaltrials.gov/show/NCT01915550> (last visited May 6, 2014).

<sup>96</sup> See CLINICALTRIALS.GOV DATABASE SEARCH, *supra* note 93.

<sup>97</sup> *Fixed Dose Study of PD 0332334 and Paroxetine for the Treatment of Generalized Anxiety Disorder*, CLINICALTRIALS.GOV, <http://clinicaltrials.gov/show/NCT00836069> (last visited May 6, 2014).

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

<sup>99</sup> Endicott & Haas, *supra* note 88.

<sup>100</sup> *Id.*

and the organizations.<sup>101</sup> But the report was consistent in finding that the most common treatment objectives of studies in pregnancy were antibiotic and anti-infective agents, including hepatitis, HIV and malaria, as well as preterm birth prevention, vitamin and nutrition supplements, diabetes and gestational diabetes, and labor induction.<sup>102</sup>

Furthermore, a 2013 study concluded that out of 558 Phase IV studies, only five, or 1%, were designed specifically for pregnant women.<sup>103</sup> This study also found that 95% of qualified studies explicitly excluded pregnant women, suggesting the exclusion to be common practice.<sup>104</sup> These results demonstrate that industry is not conducting research on pregnant women in Phase IV studies. This information highlights the importance of changing the approach to clinical research in pregnant women.

*B. Drug Case Studies Associated with Birth Defects and Industry's Response*

Physicians may fail to prescribe drugs during pregnancy because of the lack of data for drug safety, efficacy and dosage, or the fear of the unknown risk to the fetus. The failure to treat chronic illnesses such as depression, diabetes or asthma may cause significant harm to both the mother and the fetus. Pregnant women and physicians are faced with the challenging decision whether to use a medication without sufficient safety data or to stop medication. Researchers are faced with an ethical dilemma of when to enroll pregnant women in clinical research. Manufacturers lack an incentive to enroll pregnant women in research, even if safety in pregnant women may be a known issue.

The use of medicines in pregnancy is increasing due to the increasing rates of

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<sup>101</sup> *Id.*

<sup>102</sup> *Id.*

<sup>103</sup> Shields & Lyerly *supra*, note 9.

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

maternity in older women.<sup>105</sup> There is a significant prescribing of drugs known to be associated with fetal risks, with 1-4% of women being prescribed medicines considered contraindicated.<sup>106</sup>

This section discusses birth defects associated with drugs when taken during pregnancy and assesses whether the FDA and manufacturer responded appropriately.

1. Paxil Case Study: Is it Safer to take an Antidepressant or Discontinue Medication During Pregnancy?

In the case of depression, a pregnant mother is faced with the hard decision whether to stop using an antidepressant, or to continue using the antidepressant despite manufacturer warnings about possible fetal harm. Clear guidance for which treatment option is best for a pregnant mother suffering from a mental disorder that requires medication is nonexistent.

Antidepressants are widely prescribed for major depression and other psychiatric disorders and are considered the primary treatment for moderate to severe depression, although their effectiveness and safety during pregnancy have been studied infrequently.<sup>107</sup> In pregnant women with depression, antidepressants have been shown to reduce symptoms, however discontinuation has been “associated with increased risk of antenatal depressive relapses.”<sup>108</sup> Furthermore, untreated gestational depression has been associated with “pre-eclampsia, preterm delivery, low birth weight, sudden infant death, developmental delay in offspring, post-partum depression and maternal suicide.”<sup>109</sup> For

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<sup>105</sup> Thomas & Yates, *supra* note 10; See also Anne Zajicek & Jeffrey Barrett, *The grand challenges in obstetric and pediatric pharmacology*, 4 FRONTIERS IN PHARMACOLOGY 1 (2013).

<sup>106</sup> Thomas & Yates, *supra* note 10.

<sup>107</sup> William V. Bobo, et al., *The effect of regulatory advisories on maternal antidepressant prescribing, 1995-2007: an interrupted time series study of 228,876 pregnancies*, 17 ARCHIVES WOMEN'S MENTAL HEALTH 17, 18 (2014).

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

<sup>109</sup> Bobo, et al., *supra* note 107 at 18.

many years, selective serotonin reuptake inhibitors (SSRIs), “the most commonly prescribed antidepressants, were regarded as safe for use in pregnancy.”<sup>110</sup>

In 2004, the FDA issued public health advisories about the risk of perinatal complications with SSRIs and other antidepressants.<sup>111</sup> These warnings were “prompted by increasing reports of adverse neonatal outcomes associated with maternal antidepressant use including potential risk for cardiovascular malformations.”<sup>112</sup> However, the regulatory warnings did not advise against the use of antidepressants during pregnancy nor recommend antidepressant discontinuation.<sup>113</sup>

The FDA first approved Paxil, an SSRI to treat depression, in 1992.<sup>114</sup> However, Paxil has been associated with a number of birth defects. In 2005 the manufacturer of Paxil told physicians that preliminary study results suggested an increased risk of congenital malformations associated with the use of Paxil during early pregnancy as compared with other antidepressants.<sup>115</sup> The prescribing information for Paxil CR states that there are no adequate and well-controlled studies in pregnant women, and it should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.<sup>116</sup> However, lawsuits charge that the manufacturer deliberately withheld what it knew about Paxil’s dangers to developing fetuses.<sup>117</sup> The manufacturer’s motion to dismiss various products liability claims was granted with respect to all claims, except the

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

<sup>111</sup> *Id.*

<sup>112</sup> *Id.*

<sup>113</sup> *Id.*

<sup>114</sup> Susan Heylman, *New Paxil Suits Allege Birth Defect Risk*, TRIAL (Mar. 2007).

<sup>115</sup> Heylman *supra*, note 114.

<sup>116</sup> *Paxil CR Full Prescribing Information*, FDA.GOV, [http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006b1\\_08\\_paxil-label.pdf](http://www.fda.gov/ohrms/dockets/ac/04/briefing/4006b1_08_paxil-label.pdf) (last visited May 6, 2014).

<sup>117</sup> Heylman *supra*, note 114.

failure-to-warn.<sup>118</sup> Specifically, after using Paxil while pregnant, plaintiff's infant daughter died sixteen days after birth from a congenital heart defect.<sup>119</sup> After the infant's death, the manufacturer revised the warning label to indicate that there were no adequate studies of the drug in pregnant women and that one study indicated an increased risk of congenital cardiovascular malformations from use of paroxetine.<sup>120</sup>

The failure to gather consistent data about safety of antidepressant use during pregnancy is a contributing factor to the well-known SSRI birth defects and is an example of the need for evidence-based data. With this data, consistency in safety for depression and pregnancy will be uniform.

## 2. Accutane Case Study: The FDA's Response to Accutane Birth Defects

Accutane (isotretinoin) is a highly effective treatment for severe recalcitrant nodular acne, but is known to cause serious birth defects when pregnant women use the drug.<sup>121</sup> The manufacturers of Accutane and the FDA implemented a risk management program to educate women about the risk of becoming pregnant while taking this drug.<sup>122</sup> The iPLEDGE program is to prevent the use of Accutane during pregnancy and in order to obtain the drug, patients must register with iPLEDGE, and comply with a number of requirements that include completing an informed consent form, obtaining counseling about the risks and requirements for safe use of the drug, and, for women of childbearing

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<sup>118</sup> Stratford, et al., v. SmithKline Beecham Corp. et al., No. 2:07-CV-639, 2008 U.S. Dist. WL 2491965, at \*1 (Ohio Cir. Dec., June 17, 2008).

<sup>119</sup> *Id.* at \*5 (in finding that the claim was in part because defendant manufacturer actively promoted use of the drug by pregnant women).

<sup>120</sup> *Id.* at \*2. See also AM. L. PROD. LIAB. 3d § 89:71.

<sup>121</sup> Press Release, U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., *FDA and Manufacturers of Accutane and its Generics to Implement iPLEDGE Program on March 1, 2006* (Feb. 23, 2006), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108605.htm>.

<sup>122</sup> *Id.*

age, complying with necessary pregnancy testing.<sup>123</sup> This risk management program is an example of a controlled data collection environment that will decrease birth defects.

### 3. Depakote ER Case Study: Abbott's Unwillingness to Conduct Research in Pregnant Women

The FDA approved Depakote for marketing in 1983.<sup>124</sup> In 1996, Depakote (divalproex sodium), manufactured by Abbott Laboratories, was approved for the treatment of epilepsy and migraine headaches.<sup>125</sup> In 2000, Depakote ER was approved for the prevention of migraine headaches in adults.<sup>126</sup> The FDA warned Depakote ER had been associated with birth defects, specifically, spina bifida.<sup>127</sup>

In May 2013, the FDA released a Drug Safety Communication for Depakote ER, which stated a recent study showed children exposed to this class of drugs while their mothers were pregnant had decreased IQs.<sup>128</sup> This warning also stated the FDA will advise manufacturers to change the pregnancy category<sup>129</sup> for migraine use from "D" to

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<sup>123</sup> *Id.*

<sup>124</sup> *Depakote*, DRUGS.COM, <http://www.drugs.com/pro/depakote.html> (last visited May 6, 2014).

<sup>125</sup> *Depakote (divalproex sodium)*, CENTERWATCH.COM, <http://centerwatch.com/drug-information/fda-approved-drugs/drug/133/depakote-divalproex-sodium> (last visited May 6, 2014).

<sup>126</sup> *Id.*

<sup>127</sup> *Id.*

<sup>128</sup> Press Release, U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., *Valproate Anti-seizure Products Contraindicated for Migraine Prevention in Pregnant Women due to Decreased IQ Scores in Exposed Children*, (May 6, 2013), available at <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM350748.pdf>. [hereinafter 2013 DRUG SAFETY GUIDANCE]

<sup>129</sup> See Pace & Schwarz, *supra* note 6 (explaining the FDA's pregnancy risk classification system). The risk classification system is determined by the existence of human or animal data regarding the pregnancy safety of a medication, the documentation of adverse fetal outcomes in humans or animals and also by the perceived risk:benefit ratio for women. Class A: Adequate and well controlled (AWC) studies in pregnant women have failed to demonstrate a risk to the fetus. Class B: Animal reproduction studies have failed to demonstrate a risk to the fetus but there are no AWC studies in pregnant women. Class C: Animal reproduction studies have shown an adverse risk on the fetus, there are no AWC studies and humans and the benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. Class D: There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, but the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks. Class X: Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports, and the risk of the use of the drug in a pregnant woman clearly outweighs any possible benefit. *Id.* (citing KB Feibus, *FDA's*

“X.”<sup>130</sup> According to the prescribing information, Depakote ER is currently pregnancy category D for epilepsy and for manic episodes associated with bipolar disorder, and category X for prevention of migraine headaches.<sup>131</sup> The different pregnancy categories for the same product will likely lead to confusion amongst prescribers and women.

The FDA’s communication of contraindication, category X, for prevention of migraines in pregnant women does not provide clear guidance because it only warns that pregnant women taking this medication should not stop since stopping suddenly may cause life-threatening problems to the woman or baby.<sup>132</sup> The FDA stated that it is not known if there is a specific time period for harm or when the exposure may be considered to have less risk for decreased IQ in children.<sup>133</sup> This communication does not discuss the risks associated with Depakote ER for the original epilepsy indication.

The Depakote ER fetal risk knowledge gap from the approval to the subsequent black box warnings is alarming for three reasons. First, the method by which the data for fetal risk were obtained compared to the time on the market is a concern. Pregnancy registry data<sup>134</sup> in combination with drug safety warnings suggest Abbott did not engage in any proactive studies to determine the safety of Depakote ER in pregnant women.<sup>135</sup>

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*proposed rule for pregnancy and lactation labeling: improving maternal child health through well-informed medicine use*, J. MED. TOXICOL. 4(4), 284–288 (2008).

<sup>130</sup> 2013 DRUG SAFETY GUIDANCE, *supra* note 128.

<sup>131</sup> *Depakote ER Full Prescribing Information*, ABBVIE, <http://www.rxabbvie.com/pdf/dep3.pdf> (last visited May 6, 2014).

<sup>132</sup> 2013 DRUG SAFETY GUIDANCE, *supra* note 128.

<sup>133</sup> *Id.*

<sup>134</sup> See *Depakote ER Full Prescribing Information*, *supra* note 131 at 36 (noting that human data for fetal risk were obtained through a pregnancy registry of 149 women who used valproate during pregnancy as well as from published epidemiological studies).

<sup>135</sup> See Press Release, U.S. DEPT. OF HEALTH & HUMAN SERVS., FOOD & DRUG ADMIN., *FDA Drug Safety Communication: Children born to mothers who took Valproate products while pregnant may have impaired cognitive development*, (June 30, 2011), available at <http://www.fda.gov/drugs/drugsafety/ucm261543.htm>. The FDA previously communicated initial findings

The second observation is the failure to require a mandatory exposure registry.<sup>136</sup> The prescribing information states that physicians “should encourage patients to enroll in the registry in order to collect information on the effects of in utero exposure to Depakote.”<sup>137</sup> Abbott is not required to participate in the registry nor conduct further surveillance on pregnant patients taking Depakote ER.

The third observation is Abbott’s affirmative exclusion of pregnant women from clinical trials. According to the NIH database, Abbott sponsored a Phase III open label study in 2005 to determine the safety of Depakote ER in adolescents.<sup>138</sup> In order to be eligible for the study, the participant had to be male, or a non-pregnant, non-lactating female.<sup>139</sup> The NIH database yielded zero studies including pregnant women and divalproex sodium.

#### 4. Lessons Learned: If Industry, the Government and Manufacturers Aligned on Requiring Research in Pregnant Women, Could Birth Defects Decrease?

Paxil, Accutane, and Depakote ER all caused serious birth defects in some women who took these prescriptions during pregnancy. Ethical concerns regarding the safety of medication on fetuses have been a driving force in the exclusion of pregnant women from clinical studies. However, the risk that should be considered is whether to expose a consenting pregnant woman to medication in a closely monitored research setting, instead of exclusion because of an unknown fear. If data were collected earlier, documentation of

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about this risk in a June 2011 Drug Safety Communication, but the product was approved for the prevention of migraines in 2000, Abbott was aware of possible side effect of spina bifida taken during pregnancy, but did not publish information regarding malformations or lower IQ scores. It was not until eleven years later that the FDA released a safety announcement that was based on the results of an epidemiological study, which was not an Abbott study.

<sup>136</sup> See *Depakote ER Full Prescribing Information*, *supra* note 131 at 36.

<sup>137</sup> *Id.* (noting that patients have to call the North American Antiepileptic Drug Pregnancy Registry).

<sup>138</sup> *Study Designed to Evaluate the Safety of Prophylactic Depakote ER in the Treatment of Adolescents With Migraine*, CLINICALTRIALS.GOV, <http://clinicaltrials.gov/show/NCT00195806> (last visited May 6, 2014).

<sup>139</sup> *Id.*

known birth defects would decrease medication exposure and increase education.

For example, when data became available about birth defects associated with Paxil, there was an opportunity to proactively obtain birth defect data. The FDA had the ability to require postmarketing surveillance as a condition of approval for Paxil in pregnant women.<sup>140</sup> Furthermore, GSK did not provide the public with this information.

Contrast Paxil to Accutane, where the FDA took a proactive role in ensuring that women do not become pregnant while taking the drug because of known serious birth defects. Additionally, if the manufacturer was required to collect pregnancy exposure data on Accutane before the staggering number of reported birth defects, there is a higher probability for a lower number of birth defects due to a proactive role.

Lastly, in the case of Abbott, they failed to take a proactive approach to better understand known risks of exposure during pregnancy. Depakote was already associated with birth defects, but neither additional studies nor postmarketing surveillance on exposure were conducted.

#### V. IMPROVE CLINICAL RESEARCH PROTOCOLS TO INCREASE ENROLLMENT OF PREGNANT WOMEN IN STUDIES

The harms of inadequate clinical research fall enormously on pregnant women, their fetuses, and children exposed to medication *in utero*. It is clear that research does not actively recruit pregnant women for chronic conditions such as diabetes, depression or hypertension. The result of the failure to study medication in pregnant women negatively impacts society, industry, and the ability to enroll pregnant women in studies.

First, this recommendation addresses the ability to increase enrollment of

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<sup>140</sup> See OFFICE OF THE COMM’R, U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: POSTMARKETING STUDIES AND CLINICAL TRIALS – IMPLEMENTATION OF SECTION 505(O) OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT 7 (2009) (authorizes the FDA to require postmarketing studies or clinical trials at the time of approval or after approval if the FDA becomes aware of any new safety information).

pregnant women in clinical trials by examining different approaches agencies may adopt. The four approaches suggest the least inclusive to most inclusive participation of pregnant women in research: (1) agency collaboration, (2) notice and comment period for proposed rulemaking, (3) incentive based program, and (4) mandatory requirements.

*A. OWH & ORWH Collaboration to Develop Awareness, Education & Guidance*

With the education of healthcare professionals, researchers and pharmaceutical manufacturers, there is an ability to increase the enrollment of pregnant women in clinical trials. The FDA's OWH and the NIH's Office of Research on Women's Health (ORWH) must work collaboratively to issue updated guidance to communicate the importance of increasing the enrollment of pregnant women in clinical research.

First, the OWH<sup>141</sup> and ORWH<sup>142</sup> must update their mission and messaging to include *pregnant* women, not only women to eliminate the exclusionary approach of pregnant women in clinical studies. Noticeably absent from both organizations is *pregnant women* advocacy for both health and research.

Second, the OWH and ORWH must educate stakeholders and increase their awareness about the importance of pregnant women in clinical research. Awareness can be achieved by the publication of research, education, and guidelines. A collaboration of stakeholders to gather data must include guidance and decision makers, regulators,

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<sup>141</sup> *Office of Women's Health*, FDA.GOV, <http://www.fda.gov/AboutFDA/CentersOffices/OC/OfficeofWomensHealth/default.htm> (last visited May 6, 2014). OWH mission statement is to protect and advance the health of women through policy, science, and outreach and to advocate for the participation of women in clinical trials and for sex, gender, and subpopulation analyses. *Id.*

<sup>142</sup> *NIH Office of Research on Women's Health*, NIH.GOV, <http://orwh.od.nih.gov/about/index.asp> (last visited May 6, 2014). ORWH works in partnership with the 27 NIH Institutes and Centers to ensure that women's health research is part of the scientific framework at the NIH and throughout the scientific community. *Id.*

payers, providers, researchers, IRBs, ethics committees, patients, and the public.<sup>143</sup>

Third, the OWH and ORWH must publish updated policies to increase awareness among the general public and key stakeholders. The FDA is holding a public meeting in May 2014 on study methodologies to evaluate the safety of drugs during pregnancy.<sup>144</sup>

The FDA must also update their 2012 policy, *Successful Strategies for Engaging Women and Minorities in Clinical Trials*, because this policy does not address engaging pregnant women, but only offers strategies for diversity in trials by the recruitment of female physicians, trust, education through awareness, and community involvement.<sup>145</sup>

#### *B. Notice and Comment Period for Rulemaking to the Common Rule*

A notice of proposed rulemaking should be communicated about changes to the Common Rule. This notice will allow for public comment and require an answer and explanation from the OHRP. The proposed changes should remove pregnant women from the vulnerable population category and the paternal consent requirement in order to remove barriers to enrollment. The proposed changes should also adopt the FDA's guidance definition of minimal risk to the fetus in order to further clarify the term minimal risk, obtain public comment, and allow for OHRP to respond.

First, the regulations must remove pregnant women from the vulnerable population category. The regulations define criteria for IRB approval of research as “when some or all of the subjects are likely to be vulnerable to coercion or undue

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<sup>143</sup> David B. Clemow et al., *A Proposed Framework to Address Needs of Clinical Data for Informed Medication Use in Pregnancy*, 48.2 THERAPEUTIC INNOVATION & REG. SCI. 145 (2014).

<sup>144</sup> Meeting Notice, 79 Fed. Reg. 9469-02 (Feb. 19, 2014) (the purpose of this meeting is to obtain information on study approaches and methods to evaluate the safety of drugs and biological products during pregnancy in the post-approval setting; input will be used to support the revision of a guidance for industry on establishing pregnancy exposure registries).

<sup>145</sup> *Women in Clinical Trials*, FDA.GOV, <http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm131731.htm> (last visited May 6, 2014).

influence...additional safeguards have been included in the study to protect the rights and welfare of these subjects.”<sup>146</sup> It is not appropriate to categorize pregnant women as vulnerable to coercion or undue influence. Coercion is defined as compulsion by physical force or threat of physical force, and undue influence is defined as the improper use of power in a way that deprives a person of free will and substitutes another's objective.<sup>147</sup> To group all pregnant women as a vulnerable population that is susceptible to physical force or subject to a deprivation of free will is inexcusable. The difference between pregnant women and the other vulnerable populations falls under decision-making ability. One cannot reasonably believe that pregnant women, as a whole, lack the ability to make their own autonomous decisions because they are vulnerable in society.

Second, the regulations should remove the paternal consent requirement. The Department recognizes and encourages paternal involvement in this decision making process, nevertheless, in some cases the father’s consent is a barrier to participation in research.<sup>148</sup> General comments to the final rule for subpart B state “the recommendations of the National Task Force on AIDS Drug Development, the Presidential Advisory Council on HIV/AIDS, and the IOM Committee were unanimous that the consent of the father should not be a condition of the participation of a pregnant woman in research.”<sup>149</sup> The final rule also stated that some commenters described specific trials in which pregnant women were unable to participate in potentially beneficial research because they could not get paternal consent.<sup>150</sup> The informed consent process deems the woman as sufficient to make her autonomous decision to engage in research and the paternal

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<sup>146</sup> 45 C.F.R. § 46.111(b).

<sup>147</sup> Black's Law Dictionary (9th ed. 2009).

<sup>148</sup> Protection of Human Research Subjects, 66 Fed. Reg. 3878-01 at 3880.

<sup>149</sup> *Id.*

<sup>150</sup> *Id.*

consent should be removed due to it being a barrier.

Lastly, the Department should further define minimal risk. In FDA guidance, they acknowledge the definition of minimal risk is broad and state “fetal risk is considered minimal when the estimated risk to the fetus is no more than that from established procedures routinely used in an uncomplicated pregnancy or in a pregnancy with complications comparable to those being studied.”<sup>151</sup> Therefore, regulations should adopt the FDA’s proposed definition of minimal risk in order to encourage researchers and IRBs to be more inclusive in enrolling pregnant women.<sup>152</sup>

*C. Create Incentive Based Program to Increase Enrollment of Pregnant Women*

Congress should expand the six-month pediatric patent exclusivity regulation to pregnant women. This would incentivize manufacturers to conduct studies in pregnant women, similar to the studies conducted in the pediatric population.

Congress awards six months of patent exclusivity in return for conducting pediatric studies as a marketing incentive to manufacturers.<sup>153</sup> The FDA requires that the manufacturer conduct the trials in order to receive the patent exclusivity for marketing.<sup>154</sup> The exclusivity is granted for conducting a valid study even if the information collected by the manufacturer does not demonstrate an effect or difference.<sup>155</sup>

The FDA may develop, prioritize, and publish a list of approved drugs for which additional pediatric information may produce health benefits in the pediatric

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<sup>151</sup> 2004 FDA DRAFT GUIDANCE, *supra* note 70.

<sup>152</sup> See *Comment to HHS*, THESECONDWAVEINITIAIVE.ORG, [http://secondwaveinitiative.org/Comment\\_to\\_HHS.html](http://secondwaveinitiative.org/Comment_to_HHS.html) (last visited May 6, 2014) (stating “the concept of minimal risk is challenging; in the context of research in pregnancy, it has been interpreted incredibly conservatively. To give just one example, we have had experience with government officials who interpret this as ruling out pharmacokinetic studies with pregnant women – an extremely low risk study methodology that is critical to determining dosing medications in pregnant women”).

<sup>153</sup> 21 U.S.C.A. § 355a(b).

<sup>154</sup> *Id.*

<sup>155</sup> SHASHANK UPADHYE, GENERIC PHARMACEUTICAL PATENT AND FDA LAW § 12:13 (2014).

population.<sup>156</sup> To determine the drugs on the list, the FDA used several criteria, consulted with experts, and made the draft list available for public comment.<sup>157</sup> The criteria<sup>158</sup> and therapeutic category<sup>159</sup> were central to determine patent exclusivity.

There is a similar opportunity to increase the enrollment of pregnant women in research by creating a patent exclusivity incentive for manufacturers to conduct studies in pregnant women. Researchers are reluctant to conduct studies in pregnant women because of ethical concerns for adverse effects of medication exposure to the developing fetus.<sup>160</sup> If the FDA expands 21 U.S.C. § 355a to research in pregnant women, the agency can educate researchers for when it is ethically appropriate to conduct research.<sup>161</sup>

Pharmaceutical manufacturers have taken advantage of patent exclusivity for new pediatric drugs. As of February 2014, the FDA granted pediatric exclusivity for 216 pediatric studies.<sup>162</sup> An analysis of the 199 drugs that were granted exclusivity shows the predominance of top pharmaceutical companies receiving exclusivity periods for drugs.<sup>163</sup>

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<sup>156</sup> List of Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population; Availability, 63 Fed. Reg. 27733-02 (notice May 20, 1998).

<sup>157</sup> *Id.* (experts included in those in pediatric research, trade organizations, and other interested persons).

<sup>158</sup> Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, 63 Fed. Reg. 66632-01 (Dec. 2, 1998) (to be codified at 21 C.F.R. pt. 201, 312, 314, 601) (stating criteria of the drug would “be a significant improvement compared to current marketed products in the relevant pediatric population, or the drug is widely used in the pediatric population, as measured by at least 50,000 prescription mentions per year, or the drug is in a class or for an indication for which additional therapeutic options for the pediatric population are needed”).

<sup>159</sup> *Id.* (noting categories where efficacy studies are needed: oncology, neurological, acne, asthma).

<sup>160</sup> Coakley, et al., *supra* note 7 at 77.

<sup>161</sup> See 2004 FDA DRAFT GUIDANCE *supra*, note 70 (where this includes a section “Deciding Whether To Conduct A Pharmacokinetic Study In Pregnant Women.” The FDA states that ethical issues are important when considering studying drugs in pregnant women). An addition of an ethical decision making section to educate researchers about the appropriateness of the study will help overcome ethical fears.

<sup>162</sup> *Pediatric Exclusivity Granted*, FDA.GOV, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050005.htm> (last visited May 6, 2014).

<sup>163</sup> See *Id.* (according the website, GlaxoSmithKline received market exclusivity periods for seventeen drugs, Astra Zeneca had fifteen drugs and Bristol Myers and Merck both had 13 drugs. Hypertension was a common condition, but so were asthma, anxiety, and diabetes).

These data suggest that top manufacturers were able to meet requirements for research in pediatric populations when there was a potential for health benefit. Similar to pediatric research, manufacturers may choose when to conduct trials in pregnant women.

*D. Mandatory Requirements to Increase Enrollment of Pregnant Women in Clinical Research*

Congress, the FDA and the NIH have the ability to amend laws and regulations to increase the enrollment of pregnant women through the creation of new IND and NDA laws, defining subpopulation of women, and expanding pregnancy registries.

First, IND and NDA's must require an assessment in pregnant women prior to approval of the drug or biologic. Under the current law, the FDA has the authority to require a pediatric assessment, which contains data adequate to assess safety and efficacy.<sup>164</sup> This pediatric population mandate has contributed data on drug labels "concerning the safe and effective use of more than 400 drugs in neonates, infants, children, and adolescents."<sup>165</sup>

An adoption of a similar law for an assessment in pregnant women prior to approval, where scientifically appropriate, will increase evidence-based data. This law will adopt testing protocols similar to the Pediatric Research Equity Act, including allowing a waiver when a pregnant women assessment is not necessary. The pediatric population is also categorized as a vulnerable population, yet this law has proved successful in the ability to regulate and conduct clinical studies in pediatrics. Therefore, a

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<sup>164</sup> See 21 U.S.C.A. § 355c (the "Pediatric Research Equity Act" authorizes the FDA to require a pediatric assessment of a drug or biologic when there is an application for a new indication, new dosage form, a new dosing regimen, a new route of administration, or a new active ingredient. The pediatric assessment must contain data, that are adequate to assess the safety and effectiveness of product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective).

<sup>165</sup> Michael L. Christensen, *Best Pharmaceuticals for Children Act and Pediatric Research Equity Act: Time for Permanent Status*, 17 J. PEDIATR. PHARMACOL. THER. 140 (2012).

similar law must be enacted to increase pregnant women in clinical research.

Second, the FDA should expand NDA and IND demographic reporting for subgroups to include pregnant women and non-pregnant women. Federal regulations require NDA's to present effectiveness and safety data for important demographic subgroups, specifically gender.<sup>166</sup> One public comment to the FDA requested a definition for subpopulations of women because "safety, pharmacokinetic, and efficacy data for pregnant women should be presented separately from data for women who are not pregnant."<sup>167</sup> However, the FDA declined to define subpopulations of women because "it is not necessary...and usually pregnant women would only participate in clinical trials intended specifically to study drug effects during pregnancy. The data generated from such trials would, therefore, reflect use in this subpopulation of women."<sup>168</sup>

The FDA should not decline to define subpopulations of women. The response that data generated from trials that were specifically intended to study drug effects during pregnancy is unsatisfactory based on today's clinical trial landscape. Manufacturers and the NIH are not conducting any trials in pregnant women to determine safety and efficacy of drugs for chronic conditions such as diabetes and hypertension. Trials do not reflect a breakdown of subpopulations for pregnant and non-pregnant. A requirement for a trial to provide a women subpopulation is an appropriate response.

Lastly, Congress should expand the law to require pregnancy exposure registries as a condition for approval for drugs in Category C, D, or X. As part of the expansion of pregnancy exposure registries, the FDA should also issue guidance for manufacturers to

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<sup>166</sup> See 63 Fed. Reg. 6854-02, *supra* note 33 (explaining that regulations also require sponsors to tabulate in their annual reports the numbers of subjects enrolled to date in clinical studies for drug and biological products according to age group, gender, and race in INDs).

<sup>167</sup> See 63 Fed. Reg. 6854-02, *supra* note 33.

<sup>168</sup> *Id.*

become involved in the process by creating a portal for patients to enroll in a registry for a product that is C, D or X. The FDA has the authority to require drug makers to study the effects of newly approved medicines on pregnant and nursing women and newborn infants, therefore the FDA must decide if the manufacturer should be required to set up a pregnancy registry as a condition of approval.<sup>169</sup>

The FDA does not maintain the pregnancy registries, although there is a partial list available on the OWH website. The law must require registries as a condition of approval for Category C, D and X drugs as well as postmarketing surveillance.<sup>170</sup> The expansion of this law allows for the FDA to require the collection of data in pregnant women with the ultimate goal to decrease birth defects and promote awareness about the importance of obtaining evidence-based medicine in pregnancy.

#### CONCLUSION

Awareness, education, incentive programs, or mandatory requirements from DHHS will resolve the conflict of obtaining evidence-based data for prescriptions taken during pregnancy as well as increase enrollment of pregnant women in clinical trials. The harms of inadequate clinical research fall on pregnant women, fetuses, and children. Over the past twenty years, women may participate in clinical research, but as the current clinical trial landscape demonstrates, researchers and industry do not enroll or recruit pregnant women. Pregnant women must be afforded the same rights, advocacy, and data, and it is up to the industry and government to provide a different approach and ensure

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<sup>169</sup> *Registries Help Moms Measure Medication Risks*, FDA.GOV, <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm223320.htm> (last visited May 6, 2014).

<sup>170</sup> *See Novartis Patient Assistance*, NOVARTIS.COM <http://www.pharma.us.novartis.com/patient-assistance/index.shtml> (last visited May 7, 2014) (where the drug company has provided a patient assistance portal where patients may log online and manage prescriptions, diseases, and insurance). The FDA could also issue guidance to demonstrate the creation of a portal for patients to share when a medication is taken during pregnancy.

improved methodologies to clinical research.