No. 12-1094

In The Supreme Court of the United States

TERRY CLINE, *ET AL.*,

Petitioners,

v.

OKLAHOMA COALITION FOR REPRODUCTIVE JUSTICE, *ET AL.*,

Respondents.

On Petition For A Writ Of Certiorari To The Oklahoma Supreme Court

BRIEF OF *AMICI CURIAE* DR. JOHN THORP, M.D., FACOG; DR. JOHN SEEDS, M.D., FACOG; THE AMERICAN ASSOCIATION OF PRO-LIFE OBSTETRICIAN AND GYNECOLOGISTS (AAPLOG); THE CHRISTIAN MEDICAL & DENTAL ASSOCIATION (CMDA); AND THE CATHOLIC MEDICAL ASSOCIATION (CMA) IN SUPPORT OF PETITIONERS

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QUESTION PRESENTED

Oklahoma law requires that abortion-inducing drugs be administered according to the protocol described on the drugs' FDA-approved labels. The question presented is whether the Oklahoma Supreme Court erred in holding – without analysis or discussion – that this regulation is facially unconstitutional under *Planned Parenthood v. Casey*, 505 U.S. 833 (1992).

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INTEREST OF *AMICI CURIAE*[1]

Dr. John Thorp, Jr. is an obstetrician-gynecologist, board-certified in maternal and fetal medicine since 1992, licensed to practice medicine in North Carolina. He is a Fellow of the American Gynecological and Obstetrics Society and a member of the American College of Obstetricians and Gynecologists. Dr. Thorp has authored 18 book chapters and serves as a reviewer for 37 medical journals, including *The New England Journal of Medicine*, *Mayo Clinic Proceedings*, *Obstetrics & Gynecology*, *The American Journal of Obstetrics and Gynecology*, *British Journal of Obstetrics and Gynecology*, *Lancet*, *Journal of Perinatal Medicine*, and *Journal of the American Medical Association: Archives of General Psychiatry.* He has published 306 peer-reviewed articles, 155 abstracts discussing medical research, and 39 non-peer-reviewed articles, including a recent review of abortion: J. Thorp, *Public Health Impact of Legal Termination of Pregnancy in the US: 40 Years Later,* SCIENTIFICA (Dec. 2012) [hereinafter Thorp 2012].

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[1] As required by Rule 37.2(a) for the filing of this brief without motion, all parties, through their counsel of record, were given ten days' notice of the filing of this brief. The parties have consented to the filing of this brief. Pursuant to Rule 37.6, *Amici* represent that no counsel for a party authored this brief in whole or part, and no counsel or party made a monetary contribution intended to fund the preparation or submission of this brief. Printing costs for the brief were paid for by Jubilee Campaign.

Dr. Thorp received his M.D. from East Carolina University Medical School in 1983. His residency training took place at the University of North Carolina ("UNC") (Chapel Hill) School of Medicine in general obstetrics and gynecology (1983–1987). He completed his fellowship in Maternal-Fetal Medicine at UNC (Chapel Hill) School of Medicine in 1989, and earned his Master of Health Sciences Degree in Clinical Leadership from Duke University School of Medicine in 2009. At UNC (Chapel Hill) Dr. Thorp currently serves as the Hugh McAllister Distinguished Professor of Obstetrics and Gynecology in the School of Medicine and as a Professor in the Department of Maternal and Child Health in the School of Public Health; provides administrative oversight of the Family Planning Fellowship and Residency training programs, which staffs the abortion services at the UNC health center; is the Deputy Director of the Center for Women's Health Research, Cecil G. Sheps Center for Health Services Research in the Schools of Medicine and Public Health; is the Division Director of Women's Primary Healthcare, the Program Director of the Women's Reproductive Health Research Scholars Program and Research Core, and the Co-Director of the Women's Reproductive Health Research Scholars Program; and is a Fellow of the Carolina Population Center and Director of the Biomedical Core of the Carolina Population Center of UNC. Dr. Thorp is an Adjunct Professor in the Departments of Epidemiology at UNC and Tulane University.

Dr. John W. Seeds is an obstetrician-gynecologist licensed to practice medicine in Virginia. Board-certified since 1984 in maternal and fetal medicine, Dr. Seeds is a Fellow of the American Gynecological and Obstetrics Society and a member of the American College of Obstetricians and Gynecologists (ACOG), where he has served on ACOG's Ethics Committee and as its representative on the Collaborative Committee that wrote ACOG's national standards for ultrasound, the American Institute of Ultrasound in Medicine, and the American College of Radiology.

Dr. Seeds has authored 102 publications in peer-reviewed medical journals, 24 book chapters, and 18 medical abstracts, focusing on all aspects of obstetrics and gynecology, and the obstetric and gynecological use of ultrasound technology, appearing in such journals as *The New England Journal of Medicine*, *Mayo Clinic Proceedings*, *Obstetrics & Gynecology*, *The American Journal of Obstetrics and Gynecology*, *British Journal of Obstetrics and Gynecology*, *Lancet*, *Journal of Perinatal Medicine*, and *Journal of the American Medical Association: Archives of General Psychiatry*. Dr. Seeds has served as an editorial consultant for the *American Journal of Obstetrics and Gynecology* and ACOG's *Obstetrics and Gynecology*.

He received his M.D. from University of Virginia Medical School in 1972. His residency training in general obstetrics and gynecology took place at the National Naval Medical Center Bethesda, Maryland (1972–1976), and he completed his fellowship in

Maternal-Fetal Medicine at UNC in 1982. For sixteen years, Dr. Seeds served as an American Board of Obstetrician and Gynecologist examiner. Dr. Seeds currently works as the Senior Associate Dean of Professional Education Programs, as well as a Professor in the Departments of Radiology and Obstetrics and Gynecology at Virginia Commonwealth University School of Medicine (VCU). In that role, Dr. Seeds teaches medical students and residents in Obstetrics and Gynecology and Radiology, with a specialty in obstetric ultrasound. From 1997 to 2010, Dr. Seeds chaired VCU's Department of Obstetrics and Gynecology.

The **American Association of Pro-Life Obstetricians & Gynecologists (AAPLOG)** is a national organization of over 2,000 obstetricians and gynecologists and associates, including eighteen members who practice in Oklahoma. AAPLOG reaffirms the unique value and dignity of individual human life in all stages of development from conception onward. AAPLOG's mission statement includes the commitment "to educate abortion-vulnerable patients, the general public, pregnancy center counselors, and our medical colleagues regarding the medical and psychological complications associated with induced abortion, as evidenced in the scientific literature." AAPLOG has substantial expertise in the adverse medical consequences and risks involved in the use of Mifeprex as an abortion-inducing drug. AAPLOG has been a complainant to the Food and Drug Administration (FDA), documenting why the

FDA ought to stay and ultimately revoke its approval of Mifeprex and conduct a full audit of the clinical studies.

The **Christian Medical & Dental Associations (CMDA)** was founded in 1931 and today represents over 16,000 members. Members are primarily practicing physicians, including 344 physicians licensed in Oklahoma, who represent the entire range of medical specialties, including obstetrics and gynecology. Among other functions, the CMDA Medical Ethics Commission opposes on health and safety grounds, and has substantial expertise in the adverse medical consequences and risks involved in, the use of Mifeprex as an abortion-inducing drug. CMDA has been a complainant to the FDA that has documented why the FDA ought to stay and ultimately revoke its approval of Mifeprex and conduct a full audit of the clinical studies.

The **Catholic Medical Association (CMA)** has over 1,000 physicians and hundreds of allied health members nationwide, including five who practice in Oklahoma. CMA members seek to uphold the principles of the Catholic faith in the science and practice of medicine – including the belief that human life begins at conception and that, because induced abortion, including every abortion induced by Mifeprex, is a violent act interrupting the natural process of pregnancy, women are harmed by abortion physically, emotionally, and spiritually.

The individual and collective interests of the above *amici* is to ensure that the women entrusted to their care, or the care of their members, receive accurate, objective information about the health risks of any intervention provided, and that patient well-being and safety are protected. The above *amici*, individually and collectively, believe their expertise on the medical issues related to the use of Mifeprex that are implicated in this case will assist the Court in understanding the rationality of the State of Oklahoma's legislative decision to require, as a matter of health and safety, that the Mifeprex Regimen be administered as labeled by the FDA.[2]

SUMMARY OF THE ARGUMENT

Amici argue in support of the State of Oklahoma's petition for writ of certiorari. Mifeprex (also known as RU-486, a drug regimen comprised of mifepristone and misoprostol) was approved by the Food and Drug Administration for use in the U.S. on September 28, 2000. In its approval process the FDA explicitly recognized that the risks inherent in the use of the Mifeprex Regimen for abortion are dependent on the conditions and circumstances under which the Regimen is used. The FDA's approved Mifeprex

[2] The expert medical opinions expressed herein by Drs. Thorp and Seeds are theirs alone, individually, and do not represent the opinions of the institutions for whom they work or are affiliated.

protocol allows for its use up to 49 days gestation. After the drug was approved, additional "off-label" protocols were developed. Among other things, the off-label protocols involve administering the drugs up to 63 days gestation, changing the manner in which the drugs are administered, and reducing the amount of physician oversight over the administration of the drugs.

As a whole, more research into the short and long-term effects of the Mifeprex Regimen needs to be conducted, especially as it pertains to off-label uses. Existing medical data shows that medical abortion is less safe than surgical abortion. Further, the medical evidence shows that off-label uses of Mifeprex have resulted in more severe health and safety effects, including death, than the FDA-approved protocol. Given concerns about the inadequacy of reporting mechanisms for the negative side-effects of off-label uses, and the federal government's limits in regulating abortion, there is a clear need for state regulation, not only to fill the public health vacuum, but most importantly to safeguard women's health.

In 2011, the Oklahoma Legislature acted to address a serious health and safety problem caused by off-label use of the Mifeprex Regimen to induce medical abortion. This Court's abortion precedents in *Planned Parenthood of Se. Pa. v. Casey*, 505 U.S. 833 (1992), and *Gonzales v. Carhart*, 550 U.S. 124 (2007) make clear that it is within the legitimate purview of the state legislatures to impose reasonable regulations on the medical profession. Given that this law

neither bans the use of Mifeprex nor imposes a substantial obstacle to obtaining an abortion, the Oklahoma statute should be upheld.

ARGUMENT

Okla. Stat. tit. 63 § 1-729(a) (2012) is a medical regulation, enacted to protect women's health, which requires that the Mifeprex Regimen be administered consistently with the protocol approved by the FDA. As discussed below, off-label use of the Mifeprex Regimen poses significant health risks for women. Although Respondents disagree with the medical evidence, this Court has explicitly held that state legislatures are given "wide discretion to pass legislation in areas where there is medical and scientific uncertainty." *Gonzales v. Carhart*, 550 U.S. 124, 163 (2007). The regulation is rationally related to the protection of a pregnant woman's health and neither bans the use of Mifeprex nor imposes a substantial obstacle to obtaining an abortion. Thus, contrary to the decision of the Oklahoma Supreme Court, the challenged statute does not on its face impose a substantially "undue burden" on a woman's access to abortion. The Court should grant the writ and reverse the judgment below because the challenged Act is rationally related to protecting women's health based upon credible medical and scientific studies and professional experience.

I. This Is One of The Most Important Public Health Cases Since *Planned Parenthood of Se. Pa. v. Casey*.

In the forty years since *Roe v. Wade*, 410 U.S. 113 (1973), this Court has never reviewed the nature, administration, and risks of drug-induced abortions or regulations of its practice, with the possible exception of the regulation of saline abortions in *Planned Parenthood v. Danforth*, 428 U.S. 52 (1976). *Cf. Benton v. Kessler*, 505 U.S. 1084 (1992) (denying stay in challenge to import ban on RU-486). Now, saline abortions are obsolete, and drug-induced abortions are reportedly growing in the United States as a percentage of all abortions.

As one *amici* recently observed:

> in the US, one out of three women will undergo TOP [termination of pregnancy]. This makes TOP 'one of the most common medical interventions.' . . . Since 2000, medical TOP has become more widely used, building on experience from Western Europe. Medical TOP involves use of the progesterone antagonist mifepristone and the prostaglandin misoprostol. Around 10% of TOPs in the US are completed medically.

Thorp 2012, at 2 (*citing* L. Say et al., *Medical Versus Surgical Methods for First Trimester Termination of Pregnancy*, COCHRANE DATABASE SYST. REV., Art. No. CD003037 (2005); and R. Kulier et al., *Medical Methods for First Trimester Abortion*, COCHRANE DATABASE

SYST. REV., Art. No. CD002855 (2011)) [hereinafter Kulier 2011].

In 2009, Planned Parenthood "estimated" that 32% of first-trimester abortions performed in its centers in 2008 were by "medication." M. Fjerstad et al., *Rates of Serious Infection after Changes in Regimens for Medical Abortion*, 361 N. ENGL. J. MED. 145, 146 (2009). The Guttmacher Institute reported that medication abortion accounted for 17% of all non-hospital abortions and about one-quarter of abortions before nine weeks' gestation, in 2008. GUTTMACHER INST., FACTS ON INDUCED ABORTION IN THE UNITED STATES (Aug. 2011) (citing R.K. Jones & K. Kooistra, *Abortion Incidence and Access to Services in the United States*, *2008*, 43 PERSPECTIVES ON SEXUAL & REPROD. HEALTH 41 (2011)). In April 2011, the FDA "estimated" that "approximately" 1.52 million women "have used mifepristone in the US." FOOD & DRUG ADMIN., MIFEPRISTONE U.S. POSTMARKETING ADVERSE EVENTS SUMMARY THROUGH 04/30/2011, RCM 2007-525 (2011) [hereinafter FDA 2011].

Given this Court's statements in *Planned Parenthood of Se. Pa. v. Casey*, 505 U.S. 833, 846 (1992) that "the State has legitimate interests from the outset of the pregnancy in protecting the health of the woman" and that "*Roe v. Wade* was express in its recognition of the State's 'important and legitimate interests in preserving and protecting the health of the pregnant woman,'" *id.* at 875-76, and in *Gonzales v. Carhart*, 550 U.S. 124, 145 (2007) (quoting this central holding of *Roe* and *Casey*), health and safety standards for the

administration of drug-induced abortions should be constitutional on their face.

Here, the Oklahoma Supreme Court, in a *per curiam* opinion of three paragraphs, struck down the Oklahoma law with a one-sentence analysis: "The challenged measure is facially unconstitutional pursuant to *Casey*." *Okla. Coalition for Reproductive Justice v. Cline*, 292 P.3d 27, 27 (Okla. 2012). *Amici* submit the law should be upheld because it better preserves and protects the health of pregnant women than the off-label uses proposed and being practiced by the Respondents who challenge the law.

II. The Mifeprex Regimen Involves Significant Physical and Mental Health Risks.

A. The FDA Approved the Mifeprex Regimen with Restrictions.

Mifeprex was approved by the FDA for use under Subpart H, the accelerated approval regulations. *See* 21 C.F.R. §§ 314.500 to 314.560. Subpart H applies when the FDA concludes that a drug product shown to be effective can be safely used only if distribution or use is restricted, such as to certain physicians with special skills or experience. *See* Letter from the Food and Drug Administration to Population Council (Sept. 28, 2000). Thus, the FDA explicitly recognized that the risks inherent in the Mifeprex Regimen for abortion are dependent on the conditions and circumstances under which the Regimen is used. The FDA

concluded that the Mifeprex Regimen was safe enough to approve only on the condition that post-marketing restrictions applied, including adherence to the FDA protocol outlined in the Mifeprex label.

Mifeprex is a two-drug regimen of mifepristone and misoprostol, which, when effective, induces an abortion. Under the FDA-approved protocol a woman takes the first drug (mifepristone) at a doctor's office or abortion clinic. Mifepristone blocks progesterone, a hormone necessary for the uterus to provide nourishment for the embryo and fetus. Progesterone blockade causes the maternal side of the placenta to disintegrate, effectively starving the unborn child. But, mifepristone alone will cause the uterus to expel the dead embryo or fetus in only half of the times it is used. Thus, a second drug, misoprostol (a prostaglandin), is administered 36 to 48 hours later to induce uterine contractions to expel the embryo and placental tissue.

B. "Off-Label" Protocols Have Been Cited More Frequently in Adverse Events Than the FDA-Approved Protocol.

Since the Mifeprex Regimen is progressively less effective as the age of the pregnancy increases, the FDA limited its use to 49 days or less, so that the risk of ongoing and incomplete pregnancy would be minimized as much as possible. Knowing that the most common significant adverse event after using the

Mifeprex Regimen is failure to complete the abortion, the FDA protocol requires that the woman returns for a third visit approximately 14 days later for an examination to confirm efficacy and monitor bleeding. If the procedure fails, the woman is advised to undergo a surgical abortion.

The American College of Obstetricians and Gynecologists ("ACOG") states that "complete abortion rates among all regimens are highest for earlier gestations and are clinically similar in women with pregnancies up to 49 days of gestation." ACOG, *Medical Management of Abortion*, PRACTICE BULLETIN No. 67, at 6 (Oct. 2005). This means that the FDA-approved Regimen is as effective as, and thus there is no advantage to, off-label regimens for pregnancies which are less than or equal to 49 days.

The FDA considered the use of the other mifepristone/misoprostol regimens and concluded that the risk/benefit ratio did not allow for approval for use beyond 49 days. Since the FDA's approval, there have been several small studies which have looked at different protocols using a variety of different doses of mifepristone and misoprostol, but none of those studies have been analyzed by the FDA for safety and efficacy, which is required for the FDA to extend the approval to a different protocol. The situation of chaos is summed up by two recent reviews of medical abortion protocols which state:

> Meta-analysis was complicated by the fact of using 2 different pharmaceutical agents, in

> differing doses and different routes of application and most meta-analyses contain only a small number of reasonably comparable trials. We therefore focused on the primary outcome of effectiveness and were unable to draw firm conclusions on the associated side effects or relatively uncommon complications, such as continuing pregnancy or haemorrhage.[3]

In this vacuum of information on important short term safety complications (such as rates of hemorrhage, of retained tissue requiring surgical completion, or of serious infections, etc.), individual practitioners have used whatever protocol they desired, appealing to "evidence-based medicine" based on small studies. This lack of rigorous analysis of safety and efficacy is exactly the problem in medicine the FDA was authorized to address by means of the approval process. Disregard for the FDA safety and efficacy analysis of new protocols of administration allows for the use of protocols which substantially increase the health risks to women. An excellent illustration of this situation is evident in the analysis of vaginal administration of misoprostol.

Following the FDA's approval of the Mifeprex Regimen, Planned Parenthood providers began ignoring the FDA label, telling patients to administer

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[3] R. Kulier et al., *Medical Methods for First Trimester Abortion*, COCHRANE DATABASE SYST. REV., Art. No. CD002855, at 6 (2004). *See also* Kulier 2011, at 10.

the misoprostol vaginally at an increased dose of 800ug. After six deaths following vaginal misoprostol use were reported to the FDA, a CDC investigation found that these women died of a rare, rapidly fatal bacterial infection. When this news became public, Planned Parenthood changed their protocol, now telling women to hold the misoprostol in their cheek and let it dissolve (buccal administration) rather than having the women swallow the misoprostol (oral administration). *See* Gardiner Harris, *Some Doctors Voice Worry over Abortion Pills' Safety*, N.Y. TIMES, April 1, 2006, at A11; Gardiner Harris, *After 2 More Deaths, Planned Parenthood Alters Method for Abortion Pill*, N.Y. TIMES, March 18, 2006, at A10. Since that switch, an additional woman has died of overwhelming sepsis after using buccal administration. Of note, there have been *zero* deaths from overwhelming sepsis in women reported after use of the FDA protocol.

The FDA relies on "adverse event reports" as one method to determine whether to remove a drug from the market after approval. An FDA report in 2011 acknowledged at least 2,207 cases of severe adverse events, including hemorrhaging, blood loss requiring transfusion, serious infection, and 14 deaths. FDA 2011. *See also* R. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, 39 ANN. PHARMACOTHER. 1483 (2005); E. Meites et al., *Fatal Clostridium Sordelli Infections after Medical Abortions*, 363 N. ENG. J. MED. 1382 (2010).

C. There Is a Paucity of Studies Regarding the Short- and Long-Term Effects of "Off-Label" Use of the Mifeprex Regimen.

The short-term risks are directly related to the way the Mifeprex Regimen is administered, including the particular circumstances, route of administration, exact assessment of the gestational age of the pregnancy, ability of the woman to access emergency facilities in the case of hemorrhage or other life-threatening adverse event, and skill and availability of the doctor. The short-term risks of the Mifeprex Regimen approved by the FDA were published shortly before approval. *See* I. Spitz et al., *Early Pregnancy Termination with Mifepristone and Misoprostol in the United States*, 338 N. ENGL. J. MED. 1241 (1998). The failure rate of Mifepristone was eight percent with an emergency hospitalization rate of two percent. However, the short-term risks of mifepristone abortions using off-label protocols of mifepristone with vaginal and sublingual administration of misoprostol are not substantially better. Immediate complications after mifepristone abortions with vaginal or sublingual misoprostol administration were extensively studied in a recent publication from Finland. Researchers identified complications within 42 days after either medical or surgical abortion using "high-quality registry data" obtained from 42,619 women in Finland who underwent abortions using mifepristone with vaginal or sublingual misoprostol from 2000–2006 with a gestational duration of ≤63 days. The

study found: the incidence of hemorrhage is 15.6 percent following medical abortions, compared to 5.6 percent for surgical abortions; 6.7 percent of medical abortions result in incomplete abortion, compared to 1.6 percent of surgical abortions; and the rate of need for surgery following medical abortion is 5.9 percent. M. Niinimaki et al., *Immediate Complications after Medical Compared with Surgical Termination of Pregnancy*, 114 OBSTET. GYNECOL. 795, 799 (2009).

Other studies confirm the findings of the Niinimaki study, and comment on the high incidence of pain and side effects in Mifeprex abortion patients versus surgical abortion patients. Mifeprex patients report "significantly longer bleeding" and "significantly higher levels" of pain, nausea, vomiting, and diarrhea than women who have surgical abortions. J. Jensen et al., *Outcomes of Suction Curettage and Mifepristone Abortion in the United States: A Prospective Comparison Study*, 59 CONTRACEPTION 153, 156 (1999) [hereinafter Jensen 1999] (finding that a higher percentage of RU-486 patients experienced failure (18.3%) than those who had surgical abortions (4.7%)). A 2011 study found that 5.7 percent of women using Mifeprex required readmittance to a hospital while only 0.4 percent of patients required readmittance after surgical abortion. E. Mulligan & H. Messenger, *Mifepristone in South Australia: The First 1343 Tablets*, 40 AUST. FAM. PHYSICIAN 342, 343 (2011). Additional research found similar results (failure rates for medical abortion (5.2-16.0%) exceeded those

of surgical abortion (0-4.0%)). B. Winikoff et al., *Safety, Efficacy, and Acceptability of Medical Abortion in China, Cuba, and India: A Comparative Trial of Mifepristone and Misoprostol Versus Surgical Abortion*, 176 AM. J. OBSTET. GYNECOL. 431 (1997). "Women receiving mifepristone/misoprostol are more likely to require an unplanned surgical intervention than women who undergo suction curettage. They experience more discomfort with their procedure and in the follow-up interval, bleed for a longer period, and remain at risk for surgical completion curettage for several weeks." Jensen 1999, at 153. Other studies found that complications of medical abortion were severe enough that between 13-15% of women obtaining them consulted their general practitioner afterwards. H. Hamoda et al., *A Randomized Controlled Trial of Mifepristone in Combination with Misoprostol Administered Sublingually or Vaginally for Medical Abortion Up to 13 Weeks of Gestation*, 112 BJOG 1106, 1106 (2005).

The long-term risks have been inadequately studied. As reported by *amicus* Dr. Thorp and colleagues in 2005, no study of long-term risks existed, nor does any today. J. Thorp et al., *Long-term Physical and Psychological Health Consequences of Induced Abortion: Review of the Evidence*, 72 LINACRE Q. 44 (2005). But comparative risks have been reported, including vaginal bleeding in subsequent pregnancy (H. Liang et al., *Mifepristone-Induced Abortion and Vaginal Bleeding in Subsequent Pregnancy*, 84 CONTRACEPTION 609 (2011)); adverse neonatal

outcomes (X. Huo et al., *Effect of Interpregnancy Interval after a Mifepristone-Induced Abortion in Neonatal Outcomes in Subsequent Pregnancy*, 87 CONTRACEPTION 38 (2013)); and serious infection, accounting for one-third of all abortion-related deaths in the U.S. (A. Dempsey, *Serious Infection Associated with Induced Abortion in the United States*, 55 CLIN. OBSTET. GYNECOL. 888, 888 (2012)).

The short and long-term mental health risks of Mifeprex are also of concern and understudied. In general, growing evidence suggests elective abortion carries increased risks of depression, anxiety, substance abuse, and suicide. *See generally* P. Coleman, *Abortion and Mental Health: Quantitative Synthesis and Analysis of Research Published 1995-2009*, 199 BR. J. PSYCHIATRY 180 (2011). Limited research on medical abortion has reported that women experience significantly more psychological distress than those obtaining surgical abortions. Women who have medical (rather than surgical) abortions are significantly more likely to experience symptoms of posttraumatic stress, perinatal grief, bereavement, and peritraumatic emotions. Six weeks postabortion, 20% of women had significant acute stress and 39% had potential posttraumatic stress disorder, with no reduction in grief responses during the study period. C. Rousset et al., *Posttraumatic Stress Disorder and Psychological Distress Following Medical and Surgical Abortion*, 29 J. REPROD. INF. PSYCHOL. 506, 511 (2011). Women who have had medical abortions are

more likely to experience more posttraumatic stress, pain, and bleeding, and are more likely to report their abortion worse than expected. T. Kelly et al., *Comparing Medical Versus Surgical Termination of Pregnancy at 13-20 Weeks of Gestation: A Randomized Controlled Trial*, BR. J. OBSTET. GYNECOL. 1512, 1518 (2010). They are more likely to experience a significant decline in self-esteem and increase in anxiety (P. Ashok et al., *Psychological Sequelae of Medical and Surgical Abortion at 10-13 Weeks Gestation*, 84 ACTA OBSTET. GYNECOL. SCAND. 761, Tables II & III 763–64 (2005)) and regardless of which procedure is chosen, 29.9% of women who underwent an abortion had an increased risk of post-abortion depression (N. Yilmaz et al., *Medical or Surgical Abortion and Psychiatric Outcomes*, 23 J. MATERN. FETAL NEONATAL MED. 541, 543 (2010)).

D. Regulation Is Needed to Prevent Experimentation on Women of "Off-Label" Uses of the Mifeprex Regimen.

It is highly probable that there have been even more complications of the Regimen than have been reported. Reports to the FDA about complications and adverse events are voluntary. Further, a 2006 review of the Adverse Event Reports (AER) relating to the use of the Mifeprex Regimen found that the reports "relied upon by the FDA to monitor mifepristone's post-marketing safety are grossly deficient due to extremely poor quality." M. Gary & D. Harrison, *Analysis of Severe Adverse Events Related to the Use*

of Mifepristone as an Abortifacient, 40 ANN. PHARMACOTHER. 191, 191 (2006). As the Principle Deputy Inspector General of the Department of Health & Human Services told a Senate Subcommittee,

> Adverse Event Reporting systems typically detect only a small proportion of events that actually occur. They are passive systems that depend on someone linking an adverse event with the use of a product and then reporting the event. . . . Adverse Event Reports in and of themselves typically cannot generate conclusive evidence about the safety of a product or ingredient. Rather the system generates signals that FDA must assess to confirm if, in fact a public health problems exists . . . With limited information to draw upon to generate signals, it is not surprising that FDA rarely reaches the point of knowing whether a safety action is warranted to protect consumers.[4]

Other studies may present data suggesting that off-label protocols are safe, but these have not been presented to or approved by the FDA.[5] Instead, the argument has been made that "peer-reviewed"

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[4] *Hearing on Consumer Safety and Weight-Loss Supplements. Before the Subcomm. on Oversight of Gov't Mgmt., Restructuring, and the District of Columbia, S. Comm. on Gov't Affairs*, 107th Cong. (2002) (statement of Michael Mangano, Office of Inspector Gen., U.S. Dep't of Health & Human Servs.).

[5] For a more in-depth discussion, *see generally* Kulier 2011.

studies are sufficient substitute for FDA scrutiny. This is an untenable argument, because the pre-publication peer-review process does not result in the safety or efficacy analysis required by the FDA prior to approval of a Regimen, and the peer-review process itself is not immune from bias. One recent example is the poor-quality study by Planned Parenthood. K. Cleland et al., *Significant Adverse Events and Outcomes after Medical Abortion*, 121 OBSTET. GYNECOL. 166 (2013). This study claims to determine a "rate" of complications after medical abortion, yet what it really reports are the rate of complications "reported" to Planned Parenthood. Not surprisingly, the number of complications reported to Planned Parenthood facilities is a vastly different number than has been reported for other studies which are based on recorded medical registries in countries where the medical record of all citizens can be queried and reported.[6] Since peer-reviewed publications are no substitute for the safety and efficacy analysis of the FDA, which is designed to eliminate such bias, it is in the best interests of patient safety to rely on the FDA protocol in the use of mifepristone.

Besides Mifeprex, other drugs can be used to induce abortion, including "Plan B," cytotec, methotrexate, and Ella (whose chemical makeup is similar

[6] For example, this number does not capture the complications experienced by women who went elsewhere for follow-up treatment (to their own general providers, etc.), since Planned Parenthood would have no way of knowing about them.

to mifepristone). Mifepristone and Ella are both selective progesterone receptor modulators (SPRMs), meaning they block progesterone, a hormone necessary to build and maintain the uterine wall to sustain a pregnancy. An SPRM can either prevent a developing human embryo from implanting in the uterus or it can kill an implanted embryo by starving it. The Oklahoma law does not cover all of these drugs, unless they are used with the *intent* to induce an abortion. *See* Okla. Stat. tit. 63 § 1-729(a)(A)(1).

III. The Oklahoma Regulation Is Necessary Because of The Public Health Vacuum That Exists.

The federal role in abortion health practice is severely constrained. The FDA has a statutory mandate to withhold approval of any new drug application that lacks sufficient data to establish that a drug is safe and effective for its intended use, but has a very limited enforcement role after marketing. *See* 21 U.S.C. § 355(d).

In the absence of state restrictions, the Mifeprex Regimen can be and is administrated "off-label." One way in which the FDA's protocol is being ignored is through "telemedicine" abortions. Under this process, patients are placed in a room where an off-site abortion provider appears on a computer monitor (via an internet connection) and explains the medical abortion procedure. The provider never examines the woman or performs needed tests such as an

ultrasound, which is used to confirm gestational age and rule out ectopic pregnancy and which is critical to the efficacy of the mifepristone/misoprostol Regimen. The side effects of a Mifeprex abortion, *e.g.*, excessive vaginal bleeding, abdominal pain, fatigue, nausea, and dizziness can mask similar symptoms of an ectopic pregnancy. After the brief teleconference, the drugs comprising the Mifeprex Regimen are prescribed. A button is pushed and a box opens containing the drugs, which are then self-administered or administered by a nurse. The woman is sent home with the second dose of the Regimen, and no provision is made for follow-up evaluations or visits. Because the virtual visit cannot accurately assess the gestational age of the unborn child or rule out ectopic pregnancy without ultrasound, the drug is being used in an unregulated fashion, with risks to women's health. The Oklahoma statute seeks to mitigate such risks by requiring the physician to examine the patient. The law states:

> Because the failure and complications from medical abortion increase with increasing gestational age, because the physical symptoms of medical abortion can be identical to the symptoms of ectopic pregnancy, and because RU-486 (mifepristone) or any abortion-inducing drug does not treat ectopic pregnancies but rather is contraindicated in ectopic pregnancies, the physician giving, selling, dispensing, administering, or otherwise providing or prescribing RU-486 (mifepristone) or any abortion-inducing drug *shall*

> *first examine* the woman and document, in the woman's medical chart, gestational age and intrauterine location of the pregnancy prior to giving, selling, dispensing, administering, or otherwise providing or prescribing RU-486 (mifepristone) or any abortion-inducing drug.

Okla. Stat. tit. 63 § 1-729(a)(E) (emphasis added). As a further means of protecting women's health, the law also requires that "[w]hen RU-486 (mifepristone) or any abortion-inducing drug is used for the purpose of inducing an abortion, the drug must be administered in the same room and *in the physical presence of the physician* who prescribed, dispensed, or otherwise provided the drug to the patient." § 1-729a(F) (emphasis added). The Oklahoma statute reduces risks to women by ensuring that a woman has the opportunity to meet with and receive continuous care from the same abortion provider, thus decreasing the likelihood of injury from ectopic pregnancy or other medical condition which can only be diagnosed in person.

The federal government does not have general regulatory authority over abortion. Whatever its limitations or the limitations of its 2000 approval of Mifeprex, the FDA is the only independent federal agency tasked with responsibility to independently review the safety and efficacy of a drug regimen. The FDA has limited statutory authority to require controlled post-marketing studies of the safety and effectiveness of Mifeprex. In this climate, the FDA

protocol for Mifeprex is a minimal and reasonable safety standard for the states to reinforce.

The FDA protocol is the only one approved by an independent agency, based on an independent analysis of data. In the absence of federal regulation, only the states are left to monitor the public health implications of drug-induced abortion. The states have a compelling interest in regulating drug-induced abortions, given the vacuum in federal regulation and the increasing number of women selecting this type of abortion. *See Planned Parenthood v. DeWine*, 696 F.3d 490 (6th Cir. 2012) (upholding constitutionality of Ohio Law requiring adherence to FDA Protocol in use of Mifeprex Regimen). The Oklahoma regulation, enforcing the FDA protocol, is a minimal standard for patient safety.

IV. Given Oklahoma's Compelling Interest in Patient Safety, the Oklahoma Regulation Cannot Be Facially Unconstitutional under *Casey* or *Gonzales*.

In light of the documented risks, the Oklahoma regulation of drug-induced abortion is reasonable. As this Court stated in *Gonzales*, "Where it has a rational basis to act, and it does not impose an undue burden, the State may use its regulatory power to bar certain procedures and substitute others, all in furtherance of its legitimate interests in regulating the medical profession." 550 U.S. at 158. This Court stated quite plainly in *Gonzales* that "physicians are

not entitled to ignore regulations that direct them to use reasonable alternative procedures. The law need not give abortion doctors unfettered choice in the course of their medical practice, nor should it elevate their status above other physicians in the medical community." *Id.* at 163. "Medical uncertainty does not foreclose the exercise of legislative power in the abortion context any more than it does in other contexts." *Id*. at 164. Furthermore,

> [c]onsiderations of marginal safety, including the balance of risks, are within the legislative competence when the regulation is rational and in pursuit of legitimate ends. When standard medical options are available, mere convenience does not suffice to displace them; and if some procedures have different risks than others, it does not follow that the State is altogether barred from imposing reasonable regulations.

Id. at 166. The Oklahoma regulation is rationally designed to protect the health and safety of women without substantially burdening their access to abortion.

CONCLUSION

The writ should be granted and the case set for oral argument. Alternatively, the Court should summarily reverse and remand to the Oklahoma Supreme Court for reconsideration under *Planned Parenthood of Se. Pa. v. Casey* and *Gonzales v. Carhart*.

Respectfully submitted,

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