No. 14-15624

UNITED STATES COURT OF APPEALS
FOR THE NINTH CIRCUIT

PLANNED PARENTHOOD OF ARIZONA, INC., et al.,

Plaintiffs-Appellants,

v.

WILLIAM HUMBLE, Director of the Arizona Department of Health Services, in his official capacity,

Defendant-Appellee.

On Appeal from the District of Arizona, No. 14-01910
(Hon. David C. Bury)

AMICUS CURIAE BRIEF OF **32 ARIZONA LEGISLATORS** IN SUPPORT OF DEFENDANT-APPELLEE AND AFFIRMANCE OF THE DISTRICT COURT

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CORPORATE DISCLOSURE STATEMENT

Amici Arizona Legislators are not corporate entities and therefore have no corporate information to disclose.

s/ Denise M. Burke
Counsel for Amici

Dated: May 5, 2014

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STATEMENT OF INTEREST OF *AMICI CURIAE*[1]

Amici Curiae are 11 Arizona Senators and 21 Arizona Representatives who support ARIZ. REV. STAT. § 36-449.03(E)(6), Arizona's chemical abortion regulation. *Amici* seek to demonstrate their significant state interest in protecting maternal health and to refute the unfounded claims of Plaintiffs and their *amici* that the State had no justification for enacting the regulation. To the contrary, legal authority and safety and medical data, discussed herein, demonstrate that the Legislature must be afforded "wide discretion" in regulating a procedure with known risks and "safe" alternatives.

Amici include Senators Nancy Barto, Andy Biggs,[2] Chester Crandell, David Farnsworth, Gail Griffin,[3] Al Melvin, Rick Murphy, Don Shooter, Kelli Ward, Steve Yarbrough, and Kimberly Yee,[4] and Representatives John Allen, Brenda

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[1] In accordance with Fed. R. App. P. 29, *Amici* simultaneously filed a motion for leave to file the brief. No party's counsel has authored the brief in whole or in part. No party or party's counsel has contributed money intended to fund preparing or submitting this brief. No person other than *Amici*, their members, or their counsel has contributed money that was intended to fund preparing or submitting the brief.

[2] President, Arizona Senate.

[3] President Pro Tempore, Arizona Senate.

[4] Senator Yee was formerly in the Arizona House and was the lead sponsor of the bill now at issue in this case.

Barton, Sonny Borrelli, Paul Boyer, David Gowan,[5] Rick Gray,[6] John Kavanagh, Debbie Lesko, David Livingston, Phil Lovas, J.D. Mesnard,[7] Darin Mitchell, Steve Montenegro, Justin Olson, Warren Petersen, Justin Pierce, T.J. Shope, Steve Smith, Bob Thorpe, Andy Tobin,[8] and Kelly Townsend.

As Legislators who sponsored, voted for, and/or support the regulation, *Amici* have a special interest in the outcome of this case. First, *Amici* have an interest in ensuring that a constitutional law enacted by the Legislature is upheld and enforced.

Second, *Amici* have an interest in protecting the welfare of women seeking abortion in the state. As routinely affirmed by the U.S. Supreme Court, this important interest vests in the State at the outset of pregnancy.[9]

Third, *Amici* seek to demonstrate that the Legislature should be afforded the "wide discretion" that the Supreme Court has given legislatures when there is medical uncertainty about the safety of a particular abortion method.[10]

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[5] Majority Leader, Arizona House.

[6] Majority Whip, Arizona House.

[7] Speaker Pro Tempore, Arizona House.

[8] Speaker of the House, Arizona House.

[9] *See* Part I, *infra*; *see also Gonzales v. Carhart*, 550 U.S. 124, 145 (2007); *Planned Parenthood v. Casey*, 505 U.S. 833, 846 (1992) (both citing *Roe v. Wade*, 410 U.S. 113 (1973)).

Amici urge this Court to affirm the decision of the district court.

ARGUMENT

There are two general categories of abortion: surgical and chemical (or medical). Surgical abortion involves the use of instruments to empty the uterus. Examples include aspiration and dilation and evacuation (D&E). Abortion providers—including Plaintiff Planned Parenthood—consider surgical abortion in the first trimester "extremely safe." *See, e.g.*, *Planned Parenthood Southwest Ohio Region v. DeWine*, 696 F.3d 490, 494 (6th Cir. 2012); Planned Parenthood, *In-Clinic Abortion Procedures* (2014).[11] According to the Guttmacher Institute, the majority of first-trimester abortions are surgical abortions. *See* Guttmacher Institute, *Facts on Induced Abortion in the United States* (Feb. 2014).[12]

Chemical abortion, on the other hand, involves the use of drugs to induce an abortion. The recommended method of chemical abortion in the United States is the combined use of mifepristone and misoprostol. *See, e.g.*, American College of Obstetricians and Gynecologists (ACOG), *ACOG Practice Bulletin 67 Medical Management of Abortion* (Oct. 2005). In the United States, mifepristone is

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[10] *See* Part II, *infra*; *see also Gonzales*, 550 U.S. at 163.

[11] http://www.plannedparenthood.org/health-topics/abortion/in-clinic-abortion-procedures-4359.asp. All citations listed herein were last visited on April 25, 2014.

[12] http://www.guttmacher.org/pubs/fb_induced_abortion.html.

marketed under the brand name "Mifeprex," but mifepristone is more commonly referred to as "RU-486." *Mifeprex Final Printed Labeling* ("*Mifeprex FPL*").[13] Together, the administration of mifepristone and the second drug, misoprostol—the only method of chemical abortion approved by the Food and Drug Administration (FDA)—is known as the RU-486 regimen.[14] The Guttmacher Institute reports that chemical abortion accounts for only 36 percent of abortions during the first eight weeks of pregnancy. Guttmacher Institute, *supra*.

According to the FDA, there have been 2,207 reported adverse events in the United States related to use of the RU-486 regimen, including 14 deaths. Eight deaths were the result of bacterial infection, and each death followed an unapproved use of the RU-486 regimen. FDA, *Mifepristone U.S. Postmarketing Adverse Events Summary Through 04/30/11* (July 2011).[15] On the other hand, the

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[13] http://www.accessdata.fda.gov/drugsatfda_docs/label/2005/020687s013lbl.pdf.

[14] In other words, chemical abortion is a two-drug process known by several names. The first drug can be referred to as either mifepristone (the generic name), Mifeprex (the brand name), or RU-486 (the more commonly known name). For clarity, *Amici* refer to the drug regimen as the "RU-486 regimen," and will refer generally to the first drug in the regimen as "mifepristone." When reference to the brand name is necessary, such as when referring to the drug label, *Amici* will use "Mifeprex."

[15] http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM263353.pdf.

FDA has not received a single report of a woman dying from bacterial infection following the use of the FDA-approved protocol. *Id*.

Concerned that women were dying following misuse of the RU-486 regimen, state legislatures around the country sought to protect maternal health by limiting the administration of the regimen to that protocol approved by the FDA. In 2004, Ohio became the first state to enact such a law, and the Sixth Circuit Court of Appeals has determined that it does not pose an "undue burden." *See DeWine*, 696 F.3d 490 (one issue remains before the trial court).

Likewise, Texas enacted a regulation requiring that abortion providers administer abortion-inducing drugs only in the manner approved by the FDA. As here, Planned Parenthood challenged that law in federal court—but a unanimous panel of the Fifth Circuit Court of Appeals rejected Planned Parenthood's challenge, holding that the Texas regulation is not an "undue burden." *See Planned Parenthood of Greater Texas Surgical Health Services v. Abbott*, 2014 U.S. App. LEXIS 5696 (5th Cir. Mar. 27, 2014).

Based upon the same state interests expressed by the states of Ohio and Texas, the Arizona Legislature enacted ARIZ. REV. STAT. § 36-449.03(E)(6) [hereinafter "Arizona chemical abortion regulation" or "Arizona regulation"]—a regulation designed and enacted to advance maternal health by protecting women from the potentially dangerous, unapproved use of abortion-inducing drugs. That

provision requires that the RU-486 regimen be administered in the way approved by the FDA. It does not ban the use of the RU-486 regimen, nor does it ban any abortion before or after 49 days gestation. The regulation simply requires that the regimen be administered in the way deemed safest by the FDA. Other "safe" alternatives exist for women with pregnancies beyond 49 days gestation. The regulation imposes no obstacle to obtaining an abortion.

Despite the fact that eight women have died from bacterial infection after unapproved use of the RU-486 regimen—with the FDA reporting no deaths from bacterial infection following administration of the FDA-approved protocol—Plaintiffs filed this challenge, seeking to continue administering chemical abortion in a manner unapproved by the FDA.

When U.S. Supreme Court precedent is examined, it becomes clear that Plaintiffs cannot prevail on the merits. The Arizona regulation explicitly aims to protect the health and welfare of women[16]—a state interest that has been declared "important" and "legitimate" by the U.S. Supreme Court. It is an interest that vests in the state from the "outset of pregnancy." *See* Part I, *infra*. Further, the Court has determined that Arizona has wide discretion to enact protective laws where parties disagree as to the medical safety of a particular abortion procedure or

[16] The Legislature provided substantial justification for the regulation within the text of the enabling legislation, HB 2036, including findings related to maternal health. Those findings are discussed in Part III, *supra*.

method. In short, laws aimed at protecting maternal health in the midst of medical uncertainty do not pose an "undue burden." *See* Part II, *infra*.

The State relied on safety and medical data when enacting its regulation of chemical abortion—a procedure with known risks and "safe" alternatives. This data includes evidence that that FDA intended to restrict use of the RU-486 regimen for safety reasons; that chemical abortion poses significant risks; that eight women have died from bacterial infection following misuse of the RU-486 regimen, while no women have died from bacterial infection following use of the FDA-approved protocol; and that safer, "commonly used and generally accepted" alternatives to chemical abortion are available to women. *See* Part III, *infra*.

Plaintiffs may disagree with the Legislature's action in the wake of this data, but that indicates nothing more than medical disagreement between the parties—meaning that the State must be afforded "wide discretion." In light of that wide discretion, Plaintiffs cannot prevail on the merits and the preliminary injunction should be affirmed. *See* Part IV, *infra*.

I. States have a legitimate interest in protecting women's health from the outset of pregnancy.

In both *Gonzales v. Carhart* and *Planned Parenthood v. Casey*, the U.S. Supreme Court affirmed *Roe v. Wade*'s "essential" holding, which specifically included "the principle that the State has legitimate interests from the outset of pregnancy in protecting the health of the woman." *Gonzales*, 550 U.S. at 145;

Casey, 505 U.S. at 846 (both citing *Roe*). *Roe* "was express in its recognition of the State's 'important and legitimate interests in preserving and protecting the health of the pregnant woman….'" *Casey*, 505 U.S. at 876-77.

Likewise, the Court concluded in *Casey* that some interpretations of *Roe* could not be "reconciled with the holding in *Roe* itself that the State has legitimate interests in the health of the woman," and such interpretations "contradicted the State's permissible exercise of its powers." *Id*. at 871, 872. The Court then "rejected … the interpretation of *Roe* that considered all previability regulations of abortion unwarranted." *Gonzales*, 505 U.S. at 146. Such interpretations "led to the striking down of some abortion regulations which in no real sense deprived women of the ultimate decision." *Casey*, 505 U.S. at 875. Those interpretations went too far. *Id*.

Thus, instead of supporting "zero tolerance policies" that had previously been applied to some abortion regulations, a plurality of the Court adopted an "undue burden" analysis. This analysis examines whether a state regulation had the purpose or effect of placing a substantial obstacle in the path of a woman seeking an abortion of a nonviable fetus. *See Gonzales*, 550 U.S. at 166; *Casey*, 505 U.S. at 877, 878. What is at stake is the "woman's right to make the ultimate decision"—not a right to be insulated from all others in doing so. *Casey*, 505 U.S. at 877. Likewise, there is no right to be insulated from restrictions enacted to

protect her health and safety. There is no constitutional right to abortion on demand. *Id*. at 887. There is no right to an unsafe abortion.

Both *Casey* and *Gonzales* demonstrate that a reasonable medical regulation enacted to protect the woman's health is not an undue burden. In fact, "[a]s with any medical procedure, the State may enact regulations to further the health or safety of a woman seeking an abortion." *Id*. at 878. Only those restrictions that are *unnecessary* and have the purpose or effect of presenting a *substantial obstacle* impose an undue burden. *Id*.

Recently, the Fifth Circuit Court of Appeals utilized the Supreme Court's clear precedent and held that Texas' regulation requiring physicians to abide by the FDA-approved protocol when administering the RU-486 regimen is not an "undue burden." *See Abbott*, 2014 U.S. App. LEXIS 5696. Further, the court rejected Planned Parenthood's claim that chemical abortion is necessary for some women who cannot undergo surgical abortion—noting that Planned Parenthood provided no real evidence for that claim and that there is medical disagreement. *See id*. at **59-60.

Similarly, the Sixth Circuit Court of Appeals concluded that there was no evidence that the Ohio law would impose an undue burden. *DeWine*, 696 F.3d at 514. Instead, the evidence showed that women who were affected by the law's limitations obtained surgical abortions. *Id*. at 516. Relying on *Casey*, the Sixth

Circuit noted that "the Supreme Court has not articulated any rule that would suggest that the right to choose abortion encompasses the right to choose a particular abortion method." *Id*. at 514-15.

II. States have "wide discretion" to regulate abortion when there is "medical and scientific uncertainty."

In *Gonzales v. Carhart*, the Supreme Court explicitly held that state and federal legislatures are given "wide discretion to pass legislation in areas where there is medical and scientific uncertainty." *Gonzales*, 550 U.S. at 163.

The context in which the Court enunciated this standard is significant here. The Court was considering the constitutionality not of a *regulation* of a pre-viability abortion procedure, but a *complete ban* of a particular pre-viability procedure (*i.e*., partial-birth abortion). *See id*. at 156.

After recognizing that the government "has an interest in protecting the integrity and ethics of the medical profession" and declaring that the state has a "significant role to play in regulating the medical profession," the Court stated, "[w]here 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…." *Id*. at 157, 158 (emphasis added).

Noting that there were documented medical disagreements over whether the partial-birth abortion ban would impose significant health risks to women, the

Court determined that the relevant question was whether the ban could stand when such medical uncertainty persists. *Id*. at 162, 163. Citing numerous cases, the Court held that state legislatures are given wide discretion in areas where there is medical and scientific uncertainty. *Id*. at 163 (citing *Marshall v. United States,* 414 U.S. 417, 427 (1974) ("When Congress undertakes to act in areas fraught with medical and scientific uncertainties, legislative options must be especially broad")) (other citations omitted).

Importantly, the Court concluded that "[p]hysicians 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…." *Id*. at 163. In *Gonzales*, the medical uncertainty over whether the ban's prohibition created a significant health risk provided sufficient basis to conclude that the ban did not impose an undue burden. *Id*. at 164.

The Court also stated that its conclusion was supported by other considerations. First and foremost, alternatives to partial-birth abortion were available. *Id*. One alternative procedure had "extremely low rates of medical complications" and was "generally the safest method of abortion." *Id*. The Court contrasted the situation in *Gonzales* with the situation in *Planned Parenthood of Central Missouri. v. Danforth*, in which the Court invalidated a prohibition on saline amniocentesis—then the *dominant* method of second-trimester abortion. *Id*.

at 164-65 (citing *Danforth*, 428 U.S. 52 (1976)). Unlike the prohibition in *Danforth*, the prohibition at issue in *Gonzales* allowed "a commonly used and generally accepted method, so it [did] not construct a substantial obstacle to the abortion right." *Id.* at 165.

Further, the Court concluded that a "zero tolerance policy"—which would strike down legitimate abortion regulations if some part of the medical community is disinclined to follow the regulations—is too exacting a standard to impose on legislative power. *Id*. at 166. Instead, considerations of marginal safety, including the balance of risks, are within the legislative competence when a regulation is rational and in pursuit of legitimate ends. *Id*. The Court stated, "[w]hen 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*.

Simply put, when there is uncertainty over the safety of a regulated procedure and other procedures considered to be safe alternatives are available, a law cannot be invalid. *Id*. at 164-65.

III. The State relied on safety and medical data in enacting its chemical abortion regulation.

The Arizona Legislature relied on safety and medical data that support its interest in the protection of maternal health and demonstrate that it must be afforded the wide discretion guaranteed by the Supreme Court. This data includes

the following, examined in detail below: 1) the FDA intended to restrict use of the RU-486 regimen for safety reasons; 2) chemical abortion poses significant maternal health risks; 3) eight women have died from bacterial infection following misuse of the RU-486 regimen, while no women have died from bacterial infection following use of the FDA-approved protocol; and 4) standard, safer alternatives to chemical abortion are available.

In fact, the Legislature expressly delineated at least ten findings related to legal precedent, the FDA-approved protocol for the RU-486 regimen, and maternal health risks.[17] For example, the Legislature enacted a finding noting that the use of mifepristone presents significant health risks to women, including bacterial infection. The Legislature also included a finding explaining that there is an increased risk of complications following chemical abortion relative to surgical abortion, and that the risk of complications increases with gestational age. Further, the Legislature examined some of the complications and explained that the majority of RU-486-related deaths in the United States were from an atypical presentation of fatal (bacterial) infection.

Thus, the regulation is not based on mere legislative whim, but is based on safety and medical data which refute any claims that the regulation is lacking a "public health justification."

[17] These findings, the length of which makes duplication here prohibitive, can be found on pages 20-22 at http://www.azleg.gov/legtext/50leg/2r/bills/hb2036s.pdf.

A. The FDA intended to restrict use of the RU-486 regimen for safety reasons.

The FDA's intent to restrict the use of the RU-486 regimen was reflected throughout the approval process, with the authorization of the regimen explicitly conditioned upon the FDA's ability to restrict the use of the drugs. This intent continues to be specified in the Mifeprex final printed labeling (FPL), in the Patient Agreement required by the FDA, and in continued communications and safety warnings issued by the FDA.

The FDA approved the RU-486 regimen under "Subpart H," a special provision in the Code of Federal Regulations for drugs that "can be safely used *only if* distribution or use is *restricted*." 21 C.F.R. § 314.520 (emphasis added). Under Subpart H, the FDA can "require such postmarketing restrictions as are needed to assure safe use" of the drug approved. *Id*.

To put this in perspective, out of almost 1,800 New Drug Applications (NDAs) approved between 1992 and 2011, only 70 were approved under Subpart H.[18] Subpart H approvals are rare, and unlike drugs approved under the normal

[18] *See* FDA, *CDER Drug and Biologic Accelerated Approvals as of September 30, 2011*, available at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM278506.pdf; FDA, *Summary of NDA Approvals & Receipts, 1938 to the present* (2011), available at http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SummaryofNDAApprovalsReceipts1938tothepresent/default.htm. While it is unclear from

approval process, the use and distribution of Subpart H drugs is intended to be restricted by the FDA.[19] In other words, RU-486, as a Subpart H drug regimen, is not treated by the FDA like most other drugs.

Prior to approving the RU-486 regimen, the FDA informed the drug sponsor that restrictions "on the distribution and use of mifepristone are needed to assure safe use" of the regimen. FDA, *Feb. 2000 Approvable Letter*, page 5. At that time, the FDA also instructed the sponsor to use the FDA-recommended language for the product's FPL. *Id*. at 4-5. The FDA concluded that available data did not support the safety of home use of misoprostol, and the FDA *rejected* information in the FPL on self-administering misoprostol at home. U.S. Government Accountability Office, *Food and Drug Administration: Approval and Oversight of the Drug Mifeprex* (Aug. 2008), at 23 ("*GAO Report*").[20] In its approval letter, the FDA reiterated that the regimen was approved under Subpart H and outlined restrictions on use—including a required "Patient Agreement." FDA, *Sept. 2000 Approval Letter*.

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the FDA's documentation whether Subpart H drugs are excluded from its table of NDAs, *Amici* estimate conservatively that the NDAs listed in the table include any approved Subpart H drugs.

[19] While the FDA lacks an enforcement role once it restricts Subpart H drugs, it undisputedly is the states' role to regulate the practice of medicine.

[20] http://www.gao.gov/new.items/d08751.pdf.

The FPL for the RU-486 regimen outlines the FDA-approved dosage and administration of both mifepristone and misoprostol. *Mifeprex FPL, supra*. The FPL states explicitly that a woman should not use the regimen if "it has been more than 49 days (7 weeks) since" her last menstrual period began. *Id*. at 5, 9, 17.

In addition to restricting the time frame in which the RU-486 regimen is to be used, the FDA-approved FPL provides explicit dosage and administration instructions for both mifepristone and misoprostol:

> Treatment with Mifeprex and misoprostol for the termination of pregnancy ***requires*** three office visits by the patient. Mifeprex should be prescribed only by physicians who have read and understood the prescribing information. Mifeprex may be administered only in a clinic, medical office, or hospital, by or under the supervision of a physician, able to assess the gestational age of an embryo and to diagnose ectopic pregnancies….
>
> Day One: Mifeprex Administration
> Patients must read the MEDICATION GUIDE and read and ***sign the PATIENT AGREEMENT*** before Mifeprex is administered.
> Three 200 mg tablets (600 mg) of Mifeprex are taken in a single dose.
>
> Day Three: Misoprostol Administration
> The patient ***returns to the health care provider*** two days after ingesting Mifeprex. Unless abortion has occurred and has been confirmed by clinical examination or ultrasonographic scan, the patient takes two 200 µg tables (400 µg) of ***misoprostol orally***….
>
> Day Fourteen: Post-Treatment Examination
> Patients will ***return for a follow-up visit approximately 14 days after*** the administration of Mifeprex. The visit is very important to confirm by clinical examination or ultrasonographic scan that a complete termination of pregnancy has occurred.

Id. at 13-14 (emphasis added).

The "Patient Agreement"—referenced in the FPL and the September 2000 Approval letter—provides further evidence that the FDA intended to limit use of the RU-486 regimen to the FDA-approved protocol found in the FPL. Before administration of the RU-486 regimen, the patient, along with the physician, must attest to a number of statements, including the following: 1) I believe I am no more than 49 days (7 weeks) pregnant; 2) I understand that I will take misoprostol in my provider's office two days after I take Mifeprex (Day 3); and 3) I will do the following… return to my provider's office in 2 days (Day 3) to check if my pregnancy has ended. My provider will give me misoprostol if I am still pregnant. "Patient Agreement" *in Mifeprex FPL*, *supra*, at 19.

If abortion providers are administering the RU-486 regimen in an unapproved manner (*i.e.*, after 49 days and/or with the second dose in the regimen administered away from the office, as Plaintiffs admit), that means such providers are signing false documents and are having their patients sign false documents. It can hardly be claimed that the FDA mandated a signed "Patient Agreement" that it did not intend for the provider or patient to follow.

To the contrary, all FDA communications on the non-FDA-approved uses of the RU-486 regimen refer to such uses as "unapproved" or "off-label"—it never refers to these deviations as "evidence-based" nor does it ever imply that these deviations are acceptable. The regimen outlined in the Mifeprex FPL is repeated

throughout FDA communications as the only "approved" use. *See*, *e.g.*, FDA, *Mifeprex (mifepristone) Information* (July 19, 2011);[21] FDA, *Mifeprex Questions and Answers* (Feb. 24, 2010);[22] FDA, *Public Health Advisory: Sepsis and Medical Abortion* (Mar. 17, 2006).[23]

While Plaintiffs and their *amici* claim that the FDA generally approves "evidence-based" or "off-label" administration of drugs, that claim ignores this clear language from the FDA as well as its approval of the RU-486 regimen under Subpart H—meaning RU-486 is not to be treated just like any other drug. The RU-486 regimen was approved with restrictions, and it is not a departure from good medical practice for a state to require physicians to abide by the restrictions put in place by the FDA.

Moreover, rather than recommend the unapproved use of the RU-486 regimen, the FDA has stated that "[t]he safety and effectiveness of other Mifeprex

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21 http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm111323.htm.

22 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111328.htm.

23 http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/PublicHealthAdvisories/ucm051298.htm.

dosing regimens, including the use of oral misoprostol tablets intravaginally, has not been established by the FDA." FDA, *Mifeprex (mifepristone) Information, supra*; FDA, *Public Health Advisory: Sepsis and Medical Abortion, supra*. After the first four women died from bacterial infection following an unapproved use of the RU-486 regimen, the FDA issued a safety warning, noting that the deaths "involved the off-label dosing regimen" utilizing vaginal administration of misoprostol. FDA, *Public Health Advisory: Sepsis and Medical Abortion, supra*.

Thus, the FDA's actions both before and after approval of the RU-486 regimen demonstrate the agency's intent to restrict administration of this potentially dangerous regimen. This conclusion is affirmed by a memorandum published by the U.S. Department of Health and Human Services upon the approval of the RU-486 regimen. Memorandum of Department of Health and Human Services to "NDA 20-687 MIFEPREX (mifepristone) Population Counsel" (Sept. 28, 2000). In that memorandum, HHS discussed the necessity of adhering to the FPL, including the Agreements, in ensuring patient safety.

For example, HHS stated that "[b]y coupling professional labeling with other educational interventions such as the Medication Guide, Patient Agreement, and Prescriber's Agreement, along with having physician qualification requirements of abilities to date pregnancies accurately and diagnose ectopic

pregnancies (and other requirements), goals of safe and effective use may be achieved." *Id*. at 2.

Likewise, HHS stated that the Medication Guide (part of the FPL) will help "enhance ***compliance with the regimen*** for safety and efficacy." *Id*. at 4. The Medication Guide "will encourage patient adherence to directions for use. Patient ***adherence to directions for use and visits is critical to the drug's effectiveness and safety***." *Id*. (emphasis added). Similarly, HHS confirmed the importance of the "Patient Agreement," stating that the "signed agreement form will be given to the patient for her reference." *Id*. at 3. Because the Patient Agreement would be useful as a "reference" only if a woman were using the protocol outlined, commonsense indicates that the FDA intended patients to follow the protocol outlined.

HHS also reported that the drug sponsor and the FDA identified areas that contribute to drug safety and effectiveness, including "***compliance with the regimen*** by physicians and patients through education and monitoring." *Id*. at 8 (emphasis added). Further, HHS stated that returning to the healthcare provider on Day 3 for misoprostol is a "***requirement***" that assures correct administration. *Id*. at 3 (emphasis added).

B. Chemical abortion poses significant health risks to women.

As acknowledged by the Legislature in its findings, there are known maternal health risks associated with chemical abortion which warrant a state interest in protecting maternal health. For example, the Mifeprex FPL states that "[n]early all of the women who receive Mifeprex and misoprostol will report adverse reactions, and many can be expected to report more than one such reaction." *Mifeprex FPL, supra*, at 11. These risks include, but are not limited to, uterine hemorrhage, viral infections, and pelvic inflammatory disease. *Id*. at 12. In addition, mifepristone, the first drug in the regimen, interferes with the body's immune response, allowing bacteria, if present, to flourish and cause widespread, multi-organ infection. J.I. Webster & E.M. Sternberg, *Role of the hypothalamic-pituitary-adrenal axis, glucocorticoids and glucocorticoid receptors in toxic sequelae of exposure to bacterial and viral products*, J. ENDOCRINOLOGY 181:207-21 (2004); R.P. Miech, *Pathophysiology of Mifepristone-Induced Septic Shock Due to Clostridium Sordellii*, ANNALS OF PHARMOCOTHERAPY 39 (Sept. 2005).

In July 2011, the FDA reported 2,207 adverse events in the U.S. after women used mifepristone for the termination of pregnancy. FDA, *Mifepristone U.S. Postmarketing Adverse Events Summary Through 04/30/11*, *supra*. Among those were 14 deaths, 612 hospitalizations (excluding deaths), 339 blood transfusions, and 256 infections (including 48 "severe infections"). *Id*.

While some complications arising after use of the RU-486 regimen have been within the range expected, the U.S. Government Accountability Office has reported that the ***number of women dying from fatal infection is not within the expected range.*** *GAO Report*, *supra*, at 38.[24] To be clear, the GAO was referring to those deaths from bacterial infection which we now know followed an unapproved use of misoprostol. Those deaths from bacterial infection were not expected by the FDA. Again, it was the misuse of misoprostol (*i.e.*, at-home vaginal or buccal use, as opposed to oral use in a clinic or physician's office) linked to each of those deaths that *Amici* sought to prevent in order to better protect the lives of women in Arizona.

Further, the safety of the RU-486 regimen has not been tested on a large population of women, including minors or women who are heavy smokers. *Mifeprex FPL*, *supra*, at 3, 7. Yet abortion providers continue to administer or advocate for the ability to provide the RU-486 regimen to minors.

Moreover, the RU-486 regimen is contraindicated for women who do not have immediate access to emergency care, including medical facilities equipped to provide emergency treatment of incomplete abortion, blood transfusions, and

[24] "FDA officials have concluded that, ***with the exception of the cases of fatal infection***, the reported serious adverse events associated with Mifeprex have been within or below the ranges expected…." *GAO Report*, *supra*, at 38 (emphasis added).

emergency resuscitation. *Id*. at 5. Women should not use the regimen if they cannot easily get such emergency help in the two weeks following ingestion, and ACOG instructs that women are not good candidates for chemical abortion if they cannot return for follow-up visits. *Id*. at 17; AGOG, *supra*, at 6. Yet abortion advocates, like Plaintiffs, continue to advocate for the unsupervised, unapproved use of the RU-486 regimen for women in "rural areas" who do not have adequate access to healthcare.

*C. **Eight women have died from bacterial infections following misuse of the RU-486 regimen, while there are no reports of women dying from bacterial infections following use of the FDA-approved protocol**.*

As of April 2011, eight women had died of bacterial infection following use of the RU-486 regimen. FDA, *Mifepristone U.S. Postmarketing Adverse Events Summary Through 04/30/11*, *supra*. These women used a regimen of mifepristone and misoprostol that has not been approved by the FDA, and the number of deaths from bacterial infection is not within the expected range. *GAO Report*, *supra*, at 38-40 (emphasis added). Specifically, seven of the women used misoprostol (the second drug in the regimen) vaginally instead of orally. FDA, *Mifepristone U.S. Postmarketing Adverse Events Summary Through 04/30/11*, *supra*. One woman used misoprostol buccally. *Id*.

Significantly, *there are no reports of women dying from bacterial infections following administration of the FDA-approved protocol*, which, as explained above, requires oral administration of misoprostol. *Id*.

While the FDA has stated that it does not know whether using mifepristone and misoprostol in an unapproved manner *caused* the deaths associated with bacterial infection, it has repeatedly pointed out that the deaths *resulted after* unapproved use. *See* Part III.A, *supra.* Further, the FDA has never said that the unapproved use of the RU-486 regimen did *not* cause the deaths; it simply acknowledges that exact causes of the bacterial infections are unknown.[25]

Thus, when it enacted the chemical abortion regulation, the Arizona Legislature was faced with the following facts. Eight women had died from bacterial infection following unapproved use of the RU-486 regimen. These deaths were outside the range expected and sparked warnings from the FDA. On the other hand, there have been no reports of women dying from bacterial infections following the FDA-approved administration of the RU-486 regimen.

[25] In response to concerns about these fatal infections, Plaintiff Planned Parenthood stopped administering misoprostol vaginally, and started administering it buccally. *See* M. Fjerstad et al., *Rates of Serious Infection after Changes in Regimens for Medical Abortion*, N.E.J.M. 361:145-51 (2009). Regardless, without statutory regulation, there is nothing to prevent other providers from using misoprostol vaginally, nor is there anything to prevent Planned Parenthood from returning to its use of the vaginal administration.

While direct causation had not yet been established, neither had it been established that the unapproved use did not cause the deaths.

The Legislature sought to remedy a situation in which abortion providers were administering drugs in a potentially dangerous way and contrary to FDA restrictions. It enacted the chemical abortion regulation in an attempt to ensure that no other women die following unapproved use of a dangerous abortion-inducing drug regimen. At the very least, the Arizona regulation is in accord with the wide discretion given the Legislature to protect women's health and safety by regulating abortion in areas of "medical uncertainty."

D. "Commonly used and generally accepted" alternatives to chemical abortion are available.

The Mifeprex FPL requires that the RU-486 regimen be administered only through 49 days gestation. Plaintiffs, on the other hand, want to administer the regimen through 63 days gestation.

This represents a difference of two weeks—from 7 weeks to 9 weeks. During those two weeks, which are still in the first trimester and early in pregnancy, common surgical abortion alternatives are available. As such, the Arizona regulation is not an abortion ban, but rather a restriction predicated upon medical data as to which procedures can be safely used. Furthermore, Plaintiffs consider surgical abortion in the first trimester to be "very safe." *See, e.g.*, Planned Parenthood, *supra*.

Moreover, medical data demonstrates that chemical abortion actually poses more complications than surgical abortion. One peer-reviewed study found that the overall incidence of immediate adverse events is ***fourfold higher*** for chemical abortions than for surgical abortions. M. Niinimaki et al., *Immediate complications after medical compared with surgical termination of pregnancy*, OBSTET. GYNECOL. 114:795 (Oct. 2009).

In particular, hemorrhage and incomplete abortion are more common after chemical abortions. Researchers found the incidence of hemorrhage is 15.6 percent following chemical abortions, compared to 5.6 percent for surgical abortions. *Id*. Further, 6.7 percent of chemical abortions result in incomplete abortion, compared to 1.6 percent of surgical abortions. *Id*.

Yet another study found that chemical abortion failed in 18.3 percent of patients and that surgical abortion failed in only 4.7 percent of patients. J.T. Jenson et al., *Outcomes of suction curettage and mifepristone abortion in the United States: A prospective comparison study*, CONTRACEPTION 59:153-59 (1999). Patients who undergo chemical abortions also report significantly longer bleeding and higher levels of pain, nausea, vomiting, and diarrhea than women who undergo surgical abortions. *Id*.

Moreover, admissions by ACOG confirm that surgical abortion is not only an alternative to chemical abortion, but perhaps a better, safer alternative. ACOG

has admitted that chemical abortion fails more often than surgical abortion. ACOG, *supra*, at 4 (Table 2). Moreover, chemical abortion can take days or weeks to complete, but surgical abortion is complete in a shorter, predictable period of time. *Id*.[26] Thus, safer, "commonly used and generally accepted" alternatives to chemical abortion exist in the first trimester.

IV. Based on the State's interest in maternal health and its "wide discretion"—both of which are supported by safety and medical data relied upon by the Arizona Legislature—the Plaintiffs cannot prevail on the merits.

In light of the safety and medical data relied upon by the Legislature, the State of Arizona's interest in protecting women's health from potentially dangerous abortion-inducing drugs and the application of the "wide discretion" standard demonstrate that that the Plaintiffs cannot prevail on the merits.

First, the Arizona regulation falls squarely in line with the "important and "legitimate" interest in protecting women's health. *See Casey*, 505 U.S. at 878. The RU-486 regimen has known risks, and over 2,200 adverse events related to the RU-486 regimen have been reported to the FDA. Every woman who has died of bacterial infection following administration of the RU-486 regimen used the drugs in an unapproved manner. The FDA placed restrictions on the use of the

[26] Similarly, at least one study has found that women prefer the FDA-approved oral administration of misoprostol to the unapproved buccal administration used by Planned Parenthood. B. Winikoff et al., *Two distinct oral routes of misoprostol in mifepristone medical abortion: a randomized controlled trial*, OBSTET. GYNECOL. 112:1303-10 (Dec. 2008).

regimen, but abortion providers routinely and admittedly flout those restrictions. Arizona is free to enact regulations of abortion-inducing drugs in order to further the health and safety of women and help prevent future deaths. *Id*.

The district court correctly held that the regulation reflects a legitimate purpose and that the "primary, if not the sole, purpose of the statute is maternal health." *Planned Parenthood Arizona, Inc. v. Humble*, 2014 U.S. Dist. LEXIS 50869, **5-6 (Dist. Ariz. Mar. 31, 2014). As a reasonable medical protection aimed at protecting women's health and not interfering with "a woman's right to make the ultimate decision," *Casey* 505 U.S. at 887, the regulation must survive any "undue burden" challenges.

Second, the regulation is a proper extension of Arizona's "wide discretion" to enact laws when there is medical uncertainty about a procedure. As in *Gonzales*, the medical disagreement over the safety of unapproved administration of the RU-486 regimen is a sufficient basis to conclude that the regulation does not impose an undue burden. *Gonzales*, 550 U.S. at 164. Plaintiffs and the State disagree over whether the regulation will impose significant health risks to women, particularly to women Plaintiffs claim need chemical abortion (as opposed to surgical abortion) for medical reasons. Each side has its own experts and *amici*. However, as the Supreme Court noted, the relevant question is whether the regulation can stand when such medical disagreement, or "uncertainty," persists.

Gonzales, 550 U.S. at 162, 163. Importantly, it is where there is medical and scientific disagreement that states are given wide discretion to regulate procedures. *Id*. at 163.

As the district court explained, under *Gonzales* Plaintiffs must show more than mere disagreement between the parties; indeed, the presence of medical disagreement benefits the State, not Plaintiffs. *See Humble*, 2014 U.S. Dist. LEXIS 50869 at *13. The most Plaintiffs can demonstrate is that they disagree with Arizona (and its experts and *Amici*) regarding the safety of the chemical abortion regulation, and as such, Plaintiffs' claims fail under *Gonzales*.[27]

As in *Gonzales*, the State's "wide discretion" is supported by other considerations as well. For example, surgical abortion—a "commonly used and generally accepted method" of abortion—is available, and, therefore, the regulation cannot construct a substantial obstacle to the "abortion right." *Gonzales*, 550 U.S. at 164-65. In fact, unlike the situation in *Danforth*, chemical abortion is not the dominant method of abortion used in the first trimester. *See id.*

[27] There is clearly medical disagreement regarding the safety of administering the RU-486 regimen in a manner unapproved by the FDA. Recently, seven national medical organizations filed an *amicus* brief in *Planned Parenthood v. Abbott* refuting claims that unapproved use is "safe." Those *amici* included the American Association of Pro-Life Obstetricians & Gynecologists, which held the title of "special interest group" within ACOG for 40 years, from 1973 until 2013, when ACOG discontinued the designation of "special interest groups." That *amicus* brief is available at http://www.aul.org/wp-content/uploads/2013/11/13-51008-Planned-Parenthood-v-Abbott-amicus-brief-of-AAPLOG-et-al.pdf.

at 164-65 (discussing *Danforth*); Guttmacher Institute, *supra*. As noted in *DeWine*, a similar law in Ohio has not prevented women from obtaining surgical abortions. *DeWine*, 696 F.3d at 516.

The state's "wide discretion" is further supported by its "significant role" in regulating the medical profession. *Gonzales*, 550 U.S. at 157. This role includes prohibiting physicians from using a protocol that is not approved by the FDA and has been linked to the deaths of eight women. As determined in *Gonzales*, Plaintiffs do not have "unfettered choice" and they are not entitled to "ignore regulations that direct them to use reasonable alternative procedures," whether that be following the FDA-approved protocol or performing a surgical abortion. Likewise, as the Sixth Circuit noted, the abortion "right" does not encompass the right to choose a particular method of abortion. *See DeWine*, 696 F.3d at 514-15.

This role in regulating the practice of medicine includes an "interest in protecting the integrity and ethics of the medical profession." *Gonzales*, 550 U.S. at 157. Here, it is clearly not ethical for physicians to sign a "Patient Agreement" claiming that the woman is not more than 49 days gestation when he or she knows that the woman's pregnancy dates longer than 49 days. Nor is it ethical for physicians to direct women to sign documents claiming to be only 49 days pregnant when they are not. In addition to protecting women from the potentially dangerous effects of unapproved use of the RU-486 regimen, Arizona is acting to

curtail such falsifying of documents—clearly an unethical, dangerous practice in the medical field.

CONCLUSION

The Arizona chemical abortion regulation is a medical regulation enacted within the Arizona Legislature's wide discretion, intended to protect the health and welfare of women and based upon safety and medical data. Any medical disagreement raised by the Plaintiffs only serves to bolster the State's "wide discretion" and must be resolved in favor of the State. As such, there is no likelihood that Plaintiffs will prevail on the merits, and the decision of the district court should be affirmed.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I hereby certify that:

This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because this brief contains **6867** words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii).

Further, this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the type style requirements of Fed. R. App. P. 32(a)(6) because it has been prepared in a proportionally spaced typeface using Microsoft Word 2010, Times New Roman font, size 14.

s/ Denise M. Burke
Counsel for Amici

Dated: May 5, 2014

CERTIFICATE OF SERVICE

I hereby certify that I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the Ninth Circuit by using the appellate CM/ECF system on May 5, 2014.

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