[ORAL ARGUMENT NOT YET SCHEDULED]
No. 13-5069

IN THE
United States Court of Appeals
FOR THE DISTRICT OF COLUMBIA CIRCUIT

FRANCIS A. GILARDI, PHILIP M. GILARDI; FRESH UNLIMITED INCORPORATED, doing business as FRESHWAY FOODS and FRESHWAY LOGISTICS INCORPORATED,

Plaintiffs-Appellants,

v.

KATHLEEN SEBELIUS, et al.

Defendants-Appellees.

On Appeal from the United States District Court
For the District of Columbia,
Case No. 1:13-CV-00104-EGS (Hon. Emmet G. Sullivan, Judge)

BRIEF *AMICI CURIAE* OF BREAST CANCER PREVENTION INSTITUTE, POLYCARP RESEARCH INSTITUTE, and COALITION ON ABORTION BREAST CANCER IN SUPPORT OF PLAINTIFFS-APPELLANTS AND REVERSAL

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Dated: May 7, 2013

CERTIFICATE AS TO PARTIES, RULINGS, AND RELATED CASES

Pursuant to Circuit Rule 28, *Amici* make the following declarations:

A) Except for the following, all parties, intervenors, and *amici* appearing before the District Court and in this Court are listed in the Brief for Appellants:

- Abortion Breast Cancer Coalition
- American Association of Pro-Life Obstetricians & Gynecologists
- Archdiocese of Cincinnati
- Association of American Physicians & Surgeons
- Association of Christian Schools International
- Association of Gospel Rescue Missions
- Bioethics Defense Fund
- Breast Cancer Prevention Institute
- Catholic Medical Association
- Christian Legal Society
- Christian Medical Association
- Ethics & Religious Liberty Commission of the Southern Baptist Convention
- Institutional Religious Freedom Alliance
- Liberty, Life, and Law Foundation
- Life Legal Defense Foundation
- National Association of Evangelicals
- National Association of Pro Life Nurses
- Physicians for Life
- Polycarp Research Institute
- Prison Fellowship Ministries
- The C12 Group
- The National Catholic Bioethics Center
- Twenty-eight Catholic Theologians and Ethicists: Rev. Nicanor Pier Giorgio Austriaco, O.P., Ph.D., S.T.L.; Gregory R. Beabout, Ph.D.; Francis J. Beckwith, MJS, Ph.D.; J. Brian Benestad, Ph.D.; Rev. Thomas V. Berg, Ph.D.; Christopher O. Blum, Ph.D.; Holly Taylor Coolman, Ph.D.; Patrick G. Derr, Ph.D.; John Finley, Ph.D.; Michael P. Foley, Ph.D.; Alfred J. Freddoso, Ph.D.; Michael Gorman, Ph.D.; John S. Grabowski, Ph.D.; Joshua P. Hochschild, Ph.D.; Leroy Huizenga, Ph.D.; Angela McKay Knobel, Ph.D.; Matthew Levering,

Ph.D.; V. Bradley Lewis, Ph.D.; Steven A. Long, Ph.D.; Bruce D. Marshall, Ph.D.; William E. May, Ph.D.; Msgr. Kevin T. McMahon; Michael Pakaluk, Ph.D.; Alexander R. Pruss, Ph.D.; Michael Root, Ph.D.; Christopher Tollefsen, Ph.D.; Lawrence J. Welch, Ph.D.; and Christopher Wolfe, Ph.D.

B) References to the rulings at issue appear in the Brief for the Plaintiffs-Appellants.

C) Related cases appear in the Brief for the Plaintiffs-Appellants.

D) All applicable statutes, etc., are contained in the Brief for the Plaintiffs-Appellants.

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CORPORATE DISCLOSURE STATEMENT

Pursuant to Fed. R. App. P. 26 and L.R. 26.1, the Breast Cancer Prevention Institute, the Polycarp Research Institute, and the Coalition on Abortion Breast Cancer ("*Amici*"), make the following disclosures:

1) *Amici* are not publicly held corporations or other publicly held entities.

2) *Amici* have no parent corporations.

3) *Amici* have no stock of which a publicly owned corporation or other publicly held entity could own.

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CERTIFICATE IN SUPPORT OF SEPARATE BRIEF

Under Circuit Rule 29(d), "[*a*]*mici curiae* on the same side must join in a single brief to the extent practicable." Counsel for *Amici* certifies that this separate brief is necessary to demonstrate that the Institute of Medicine Report relied on by the government completely ignored a large body of highly relevant medical literature that reveal significant increased risks of breast, cervical and liver cancers and other serious diseases experienced by women who use hormonal contraceptives. This evidence is presented to show that the HHS Mandate fails the RFRA requirement that it "further" the asserted government interest in promoting women's health because these drugs *increase* risk of disease instead of decreasing it. Counsel for *Amici* is not aware of any party or other *amicus* in this Court that addresses this specific expertise and interest of *Amici*.

/s/ Dorinda C. Bordlee
Counsel of Record for *Amici Curiae*

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GLOSSARY

AAPLOG: American Association of Pro-Life Obstetricians and Gynecologists

ACA: Affordable Care Act

FDA: Food and Drug Administration

HHS: U.S. Department of Health & Human Services

HIV: human immunodeficiency virus

HRSA: the Health Resources and Services Administration

IOM: Institute of Medicine

Mandate: Defendants' regulatory mandate implementing the provision in the ACA requiring that all private insurance plans "provide coverage for and shall not impose any cost sharing requirements for . . . preventive care and screenings [for women]"

NCI: National Cancer Institute

RFRA: Religious Freedom & Restoration Act

STI: sexually transmitted infection

INTEREST OF AMICI CURIAE[2]

Breast Cancer Prevention Institute (BCPI) is a non-profit corporation that educates healthcare professionals and the general public through research publications, lectures, and internet resources about ways to reduce the surge in breast cancer incidence attributable to avoidable risks. BCPI is directed by Angela Lanfranchi, M.D., F.A.C.S., a breast surgeon and graduate of the Georgetown School of Medicine (M.D. 1975).

The **Polycarp Research Institute** is a non-profit organization dedicated to the promotion and dissemination of high-quality research designed to enhance the physical and psychological condition of mankind consistent with a natural law ethic. It is directed by Chris Kahlenborn, M.D., lead author of the October 2006 *Mayo Clinic Proceedings* article entitled, "Oral Contraceptive Use as a Risk Factor for Premenopausal Breast Cancer: A Meta-analysis."

Coalition on Abortion/Breast Cancer is an international women's organization whose purpose is to protect the health and save the lives of women by educating and providing information on underreported risk factors for breast cancer, such as abortion and hormonal contraceptives.

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[2] Pursuant to Cir. Rule 29, counsel certifies that all parties have consented to the filing of this brief, and further certifies that no party or party's counsel authored this brief in whole or in part, or contributed money that was intended to fund the brief.

Amici have an interest in bringing this Court's attention to the fact that, in promulgating the HHS Mandate, the Government disregarded the large body of relevant, widely available, scientifically sound, scholarly research of significantly increased health risks arising from the use of hormonal contraceptive and abortifacient drugs.[3] For this reason, the Government cannot demonstrate that application of the HHS Mandate to a religiously objecting employer meets the RFRA requirement that it be "in furtherance of a compelling governmental interest" – particularly its asserted interest in expanding access to "preventive" health services. Indeed, the HHS Mandate fails the most important test of showing a compelling interest in preventive medicine: it *increases* risk of serious disease instead of decreasing it.[4]

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[3] The term "contraceptive" as used in this brief reflects terminology used by the Government in the HHS Mandate. *Amici*, however, acknowledge the Plaintiffs' religious objection to the capacity of some of the so-called "contraceptive" drugs and devices to terminate the life of a human being at the embryonic stage of development before implantation and thus act as an abortifacient. *See e.g.*, Miech, R, *Immunopharmacology of ulipristal as an emergency contraceptive*, Intl Journal of Women's Health 3:391 (2011)("When unprotected intercourse and the administration of ulipristal occur at or within 24 hours of ovulation, then ulipristal has an **abortifacient** action.")(emphasis added).

[4] Medical and science advisors who assisted in the survey of studies presented in this brief include **John M. Thorp, Jr., M.D.,** women's health researcher, professor, and ObGyn director of the UNC-Chapel Hill Women's Primary Healthcare; **Mary Davenport, M.D.,** obstetrician/gynecologist and president of AAPLOG; **Angela Lanfranchi, M.D., F.A.C.S.,** breast surgical oncologist, and co- founder of the Breast Cancer Prevention Institute; **Maureen L. Condic, PhD,** research scientist at the University of Utah; and **Joel Brind, PhD,** scientist and

SUMMARY OF THE ARGUMENT

Plaintiffs argue that the HHS "preventive services" mandate ("HHS Mandate")[5] cannot meet the test of the Religious Freedom Restoration Act (RFRA), 42 U.S.C. §2000. Specifically, Plaintiffs point to the existence of numerous exemptions, from either the Mandate or the entire Affordable Care Act, as evidence that the Mandate does not "further a compelling governmental interest."

Amici bring to this Court's attention further grounds for finding that the HHS Mandate violates RFRA. The Government cannot meet its burden of demonstrating that imposition of the HHS Mandate on every health plan, whether group or individual, furthers any compelling governmental interest, particularly the asserted interests of promoting women's health.

Amici present a survey of the robust body of highly relevant medical evidence, completely ignored by the Government, indicating that hormonal contraceptives have biological properties that significantly increase women's risks of breast, cervical, and liver cancer, stroke, and a host of other diseases including

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professor at Baruch College in the City University of New York system. All universities are listed for purposes of identification only; this brief in no way represents the views of the named universities, nor of any of its employees.

[5] *Certain Preventive Services under the Affordable Care Act* ("the HHS Mandate"), finalized at 77 Fed. Reg. 8725 (Feb. 15, 2012).

the acquisition and transmission of human immunodeficiency virus (HIV). These increased risks have been recognized not only by other agencies of the Government itself, but also by reputable national and international medical authorities, including the research arm of the World Health Organization which has classified combined oral contraceptives as "Group 1: Carcinogenic to Humans." *See infra* at 7 n. 11, 9.

The 2011 Institute of Medicine report is empirically unsound because it completely fails to cite, acknowledge, balance or even mention the large body of medical literature surveyed in this brief showing significantly increased risks of prevalent cancers and other serious diseases. Therefore, the HHS Mandate utterly fails the RFRA test of "furthering" the asserted governmental interest in promoting women's "preventive" health.

ARGUMENT

I. Because The HHS Mandate Includes Hormonal Contraceptives that Significantly Increase Risks of Serious Disease, It Cannot Further a Compelling Interest in Promoting Women's Health Under RFRA.

In this Section, *Amici* present a survey of the large body of highly relevant peer-reviewed scientific research – completely absent from the IOM report relied on by the government[6] – that demonstrates the significantly increased health risks associated with the mandated drugs. Rather than address and balance the significantly increased risks of breast, cervical and liver cancers, or even the increased risks of HIV and other life-threatening diseases outlined below, the 2011 IOM report selectively focused only on the benign "non-contraceptive benefits of hormonal contraception includ[ing] treatment of menstrual disorders, acne or hirsutism (excessive hairiness on women), and pelvic pain."[7] Where the IOM Report does address cancer risks, it selectively cites studies that show cancers that contraceptives may help prevent, but that occur with much lower incidence and mortality than the cancer risks it increases. *See* Section C, *infra.*

In light of the devastating health dangers revealed in the studies presented

[6] Institute of Medicine, *Clinical Preventive Services For Women: Closing the Gaps* (2011) ("IOM Report").

[7] 2011 IOM Report at 107.

below, the hormonal contraceptives required under the Mandate "fail the most important test of preventive medicine: they increase risk of disease instead of decreasing it."[8] Therefore, the Government has not demonstrated and cannot demonstrate that application of the HHS Mandate to religious objectors "furthers a compelling governmental interest" in women's preventive healthcare as required by RFRA.

A. Serious Health Risks of Oral Contraceptive Pills

Women in our pluralistic society remain free to face the attendant health risks that come with choosing to use hormonal contraceptives that are FDA-approved as effective for the intended use of avoiding pregnancy. However, more than a dozen drugs have been taken off the market since 1997 due to severe side-effects, injuries or deaths.[9] Thus, FDA-approval is not the final word on safety, nor is FDA-approval dispositive in the HHS inquiry of whether a drug should be mandated as "preventive" healthcare. Indeed, media reports regularly document FDA scandals and controversies.[10]

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[8] Rebecca Peck, M.D., C.C.D. and Charles W. Norris, M.D., *Significant Risks of Oral Contraceptives (OCPs)*, 79(1) The Linacre Quarterly 41, 42 (February 2012).

[9] PBS Frontline, *Dangerous Prescription* (November 2003), available at http://www.pbs.org/wgbh/pages/frontline/shows/prescrption/etc/synopsis.html.

[10] In 2012, the *Washington Monthly*, which conducted an investigation with the assistance of the *British Medical Journal*, said the FDA neglected in December 2011 to give a report prepared by former FDA commissioner Dr. David Kessler to the advisory committee responsible for reviewing the safety of products containing

When imposing the HHS Mandate of hormonal contraceptives, the government relied on a severely deficient report issued in 2011 by the Institute of Medicine. *See* n. 5, *supra.* It is astounding that this report on women's "preventive services" completely fails to cite or even attempt to explain away the evaluation of the World Health Organization's "International Agency for Research on Cancer Working Group" which concluded, "There is sufficient evidence in humans for the carcinogenicity of combined oral estrogen–progestogen contraceptives."[11]

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the hormone drospirenone, which Bayer uses in its oral contraceptives known as Yaz and Yazmin. As an expert witness in a lawsuit filed against Bayer on behalf of plaintiffs claiming to have been injured by those Bayer oral contraceptives, Dr. Kessler cited Bayer's internal corporate reports and accused it of concealing data showing blood clot risks among users of those drugs.

According to the *Washington Monthly*, "A series of studies published in *BMJ* have shown that users of pills containing drospirenone have an increased risk of blood clots, which can cause deep vein thrombosis, pulmonary embolism, stroke, heart attack and death. And thousands of women have filed a lawsuit against Bayer, saying they were injured by Yaz or Yasmin. . . . The FDA's decision not to reveal its advisors' relationships with the drugs' manufacturers and Bayer raises serious questions about the agency's treatment of potential conflicts of interest, a historically problematic area for the department." Lenzer J and Epstein K. *The Yaz men: Members of FDA panel reviewing the risks of popular Bayer contraceptive had industry ties*, Washington Monthly (January 9, 2012), available at http://www.washingtonmonthly.com/ten-miles-square/2012/01/the_yaz_men_members_of_fda_pan034651.php# (last visited April 29, 2013).

[11] World Health Organization, International Agency for Research on Cancer (IARC) 2007 Monograph 91. *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Combined Estrogen-Progestogen Contraceptives and Combined Estrogen-Progestogen Menopausal Therapy*, *available at*

The following is a non-exhaustive survey of the completely ignored but highly relevant medical studies documenting the cancer risks and significantly increased health risks of other serious and life-threatening diseases:

1. **Higher risk of heart attack, stroke & cardiovascular complications.** Among women with no conventional risk factors for heart disease, those who take oral contraceptives have twice the risk of heart attack.[12] Those with hypertension had five times the risk; those who smoked, 12 times the risk; those who had diabetes, 16 times the risk; those who had high cholesterol, 23 times the risk.[13] A meta-analysis of 16 studies found that women who used oral contraceptives had nearly three times the risk of ischemic stroke; for those with risk factors such as high blood pressure or migraine headaches, the risk was significantly higher.[14] Hormonal contraceptives also lead to significantly higher incidence of deep

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http://monographs.iarc.fr/ENG/Monographs/vol91/mono91.pdf (last checked May 7, 2013).

[12] B.C. Tanis et al., *Oral contraceptives and the risk of myocardial infarction*, 345 New England Journal of Medicine 1787 (2001).

[13] *Id.*

[14] L.A. Gillum, *Ischemic stroke risk with oral contraceptives*, 284 JAMA 72 (2000).

venous thrombosis[15] and pulmonary embolism.[16]

2. **Higher risk of breast cancer.** The World Health Organization's International Agency on Research of Cancer (IARC) 2007 report concludes that estrogen-progestin combination drugs (the Pill) are a Group 1 carcinogen for breast, cervical, and liver cancers.[17] A 2006

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[15] A. van Hylckama Vlieg et al.,*Venous thrombotic risk of oral contraceptives, effects of oestrogen does and progestogen type: results of the MEGA case-control study*, 339 BMJ 2921 (2009).

[16] O. Lindegaard et al., *Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogens. Danish cohort study 2001-9*, 343 BMJ 6423 (2011).

[17] International Agency for Research on Cancer (IARC) 2007 Monograph 91, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Combined Estrogen-Progestogen Contraceptives and Combined Estrogen-Progestogen Menopausal Therapy* at 175, *available at* http://monographs.iarc.fr/ENG/Monographs/vol91/mono91.pdf:

> There is *sufficient evidence* in humans for the carcinogenicity of combined oral estrogen–progestogen contraceptives. This evaluation was made on the basis of increased risks for cancer of the breast among current and recent users only, for cancer of the cervix and for cancer of the liver in populations that are at low risk for hepatitis B viral infection.
>
> There is *evidence suggesting lack of carcinogenicity* in humans for combined oral estrogen–progestogen contraceptives in the endometrium, ovary and colorectum. There is convincing evidence in humans for their protective effect against carcinogenicity in the endometrium and ovary.

It is telling that the underlying research supporting the protective effect in the second paragraph was mentioned in the IOM Report, while the underlying research supporting *increased* risks for certain prevalent cancers was never even mentioned. To be clear, this authoritative and highly relevant WHO report was never once mentioned in the IOM Report.

meta-analysis published in the journal *Mayo Clinic Proceedings* showed a 44% increased risk of premenopausal breast cancer in women who took oral contraceptives before first full term pregnancy.[18] A 2009 study showed a 3.2-fold increased risk of triple negative breast cancer, the most difficult and deadly form of breast cancer to treat, in women taking oral contraceptives; and the same study showed an even more alarming 6.4-fold increased risk of that deadly form of breast cancer in teenagers who started taking oral contraceptives before age 18.[19] And it is important to note that although the risk of uterine and ovarian cancers appears lower for women taking contraceptives, there is four times more breast cancer in women than uterine and ovarian cancers combined.[20]

3. **Higher risk of cervical cancer.** The Government's own National Cancer Institute (NCI) recognized studies showing a threefold to fourfold increased risk of cervical cancer:

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[18] C. Kahlenborn et al., *Oral contraceptive use as a risk factor for premenopausal breast cancer: A meta-analysis*, 81 Mayo Clinic Proc. 1290 (2006).

[19] J. Dolle et al., *Risk factors for triple negative breast cancer in women under the age of 45*. 18 Cancer Epidemiol. Biomarkers Prev.1157 (2009).

[20] *See Cancer Statistics by Cancer Type*, Centers for Disease Control. Available at: http://www.cdc.gov/cancer/dcpc/data/types.htm (last visited September 20, 2012).

> In a 2002 report by the International Agency for Research on Cancer … data from eight studies were combined to assess the association between oral contraceptive use and cervical cancer risk among women infected with the human papillomavirus (HPV). Researchers found a nearly threefold increase in risk among women who had used oral contraceptives for 5 to 9 years compared with women who had never used oral contraceptives. Among women who had used oral contraceptives for 10 years or longer, the risk of cervical cancer was four times higher.[21]

4. **Higher risk of liver tumors/cancer.** As stated in the Government's own NCI Factsheet, "Oral contraceptive use is associated with an increase in the risk of benign liver tumors [that] have a high risk of bleeding or rupturing." Moreover, "[s]ome studies have found that women who take oral contraceptives for more than 5 years have an increased risk of [malignant liver tumors known as] hepatocellular carcinoma, but others have not." [22]

5. **Greater susceptibility to sexually transmitted infections.** Women taking oral contraceptives are twice as likely to be infected with the genital human papillomavirus (HPV) virus, leading to cervical cancer,

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[21] National Cancer Institute: Oral Contraceptives and Cancer Risk (March 21 2012) *citing* V. Moreno et al., *Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study*, 359 Lancet 1085 (2002).

[22] *Id.*, *citing* C. La Vecchia and A. Tavani, *Female hormones and benign liver tumors*. 38 Digestive and Liver Disease 535 (2006).

as women not taking oral contraceptives.[23] While the studies on HIV risk and *oral* contraceptives show mixed results, one well-known study finds that women taking the pill are 60% more likely to be infected with the HIV virus than those who are not.[24] In addition to physiological changes caused by hormonal contraceptives leading to increased susceptibility to sexually transmitted infections (STIs), recent studies indicate that increased access to emergency contraceptives leads to behavioral changes, i.e., increased risk-taking in sexual behavior, that not only cancels out any decrease in the rate of unplanned pregnancy among adolescents, but also drives up the rate of STIs.[25]

B. Serious Health Risks of Long-Acting Contraceptives

As might be predicted by standard microeconomic theory, the "no-cost" element of the HHS Mandate will not only increase use of low-cost pills and emergency contraceptives, it will also increase incentives for women and adolescents to choose the previously cost-prohibitive "long-acting methods," such

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[23] S. Franceschi et al., *Genital warts and cervical neoplasia: an epidemiological study*, 48 *Br. J. Cancer* 621 (1983).

[24] C.C. Wang et al., *Risk of HIV infection in oral contraceptive pill users: a meta-analysis*, 21 JAIDS 51 (May 1, 1999).

[25] See S. Girma et al., *The impact of emergency birth control on teen pregnancy and STIs*, 30 Journal of Health Economics 373 (2011).

as injectable contraceptives, implants, and intrauterine devices (IUDs).

According to *A Pocket Guide to Managing Contraception* (*MC*),[26] methods of long-acting contraception include:

(1) **ParaGard© Intrauterine Copper IUD:** The copper IUD can result in **uterine perforation** and other malpositioning that can result in **increased bleeding or pain**, and **injury or damage to the surrounding organs**.[27]

(2) **Mirena© levonorgestrel-releasing IUD:** Unlike ParaGard©, which contains no steroidal hormones, the Mirena© IUD releases levonorgestrel (LNG) into the uterine environment. In addition to risks of **uterine perforation**, which were the subject of a warning letter sent by FDA to the manufacturer Bayer, Mirena has been linked to **ovarian cysts**, a higher profile for **pelvic inflammatory disease** (PID), and irregular bleeding. Also, in the rare case in which a woman conceives while using the Mirena, a resultant loss of pregnancy and a **possible permanent loss of fertility** may result.[28]

(3) **Implanon©:** This device is a plastic implant rod containing progestogen etonogestrel which is surgically inserted under the skin of the upper arm; it

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[26] N. Zieman, R.A. Hatcher, et al., *A Pocket Guide to Managing Contraception,* Tiger, GA: Bridging the Gap Foundation, 2010, at 37. "*Managing Contraception*" or *MC* is a condensed version of the primary medical textbook on contraception—R.A. Hatcher et al., *Contraceptive Technology* (20th rev. ed.). Atlanta, GA: Ardent Media, Inc., 2011.

[27] K.P. Braaten et al., *Malpositioned IUDs: When you should intervene (and when you should not)*, 24(8) OBG Management 39 (2012), citing B.R. Bernacerraf et al. *Three-dimensional ultrasound detection of abnormally located intrauterine contraceptive devices which are a source of pelvic pain and abnormal bleeding* 34(1) Ultrasound Obstet. Gynecol. 110 (2009).

[28] Mirena® Label, Warnings and Precautions; *See also* Uterine Perforation Risk from Mirena, *available at* http://www.womens-health.co.uk/uterine-perforation-risk-from-mirena.html.

replaced Norplant© which is no longer marketed in the U.S., after over 50,000 women filed lawsuits—including 70 class actions—over severity of side effects.[29] In addition to **ectopic pregnancy** risks, the manufacturer warning reports "serious thromboembolic events, including cases of **pulmonary emboli (some fatal)** and **strokes**, in patients using IMPLANON."[30]

(4) **Depo-Provera©:** This is an injectable progestogen intended to last up to three months. A 2012 study reveals that there are now five studies "conducted over a diverse group of countries" that report an increased risk of breast cancer whose upper range is **more than doubled** in women who used DepoProvera for more than 12 months.[31] Moreover, in addition to this injection's **black box warning on loss of bone mineral density**, Depo-Provera use has been shown to result in a **doubled risk of acquiring and transmitting HIV**, as discussed below.

In October 2011, the *New York Times* gave front-page coverage to the rigorous Heffron study[32] that had been published in a prestigious peer-reviewed medical journal after the study's presentation had raised alarm months earlier at an international AIDS conference. The Heffron study resulted in convincing findings

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[29] CT, *supra* n. 38.

[30] Implanon© Warnings, *available at* http://www.implanon-usa.com/en/HCP/learn-about-it/get-the-facts/warnings/index.asp.

[31] C. Li et al., *Effect of Depo-Medroxyprogesterone Acetate on Breast Cancer Risk among Women 20 to 44 Years of Age*, 72(8) Cancer Res. 2028 at n.4-7(Apr. 15 2012)("with the addition of the results reported here, there are now 5 studies conducted over a diverse group of countries that have observed that recent DMPA use is associated with a 1.5- to 2.3- fold increased risk of breast cancer.")

[32] R. Heffron et al., *Use of hormonal contraceptives and risk of HIV-1 transmission: a prospective cohort study*, 12 Lancet Infect Dis. 19 (2012) (published online October 2011).

that injectable contraceptives have "biological properties" that appear to "*double* the risk that women will become infected with H.I.V.," and further finding that "when it is used by H.I.V.-positive women, their male partners are *twice as likely to become infected* than if the women had used no contraception."[33]

The study focused on Depo-Provera, a drug covered by the HHS Mandate. Of particular note is a statement by the director of the women and foreign policy program at the Council on Foreign Relations: *"If it is now proven that [injectable] contraceptions are helping spread the AIDS epidemic, we have a major health crisis on our hands."*[34]

C. The IOM Report Ignores the Fact that the Incidence of the Cancers that Combined Oral Contraceptives Cause Far Exceed the Incidence of the Cancers that they May Prevent, and also Ignores the Increased Risk to Teenage Girls.

The 2011 IOM Report is completely oblivious to the above outlined host of adverse health consequences and increased cancer risks resulting from the use of hormonal contraceptives it claims will promote women's health. The only consequences the 2011 IOM Report discusses are "side effects" (which it says are "generally considered minimal"[35]) and death rates that can be directly linked to contraceptive use.[36] It completely ignores the range of health risks between those

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[33] Pam Belluck, *Contraceptive Used in Africa May Double Risk of H.I.V.*, N.Y. Times, October 3, 2011 (covering Heffron study, *supra*)(emphasis added).

[34] *Id.* (emphasis added).

extremes, even though the Government itself acknowledges these risks on the National Cancer Institute websites, and indeed funds many of the studies discussed above through the National Institutes of Health.[37]

In an amazing display of bias, the only mention by the 2011 IOM report regarding cancer risks are those that oral contraceptives may prevent – namely endometrial and ovarian cancer.[38] In other HHS Mandate challenges, the Government's amici have also pointed to a possible reduction in the risk of colon cancer. But as explained below, even if the disputed preventive effect of oral contraceptives on colon cancer risk is included, the incidence of the cancers that combined oral contraceptives cause (breast, liver and cervix) far exceed the incidence of the cancers that oral contraceptives may prevent (colon, endometrium and ovaries) in the United States.

- **The IOM Report Ignored Studies Showing Increased Incidence of Serious Cancers**

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[35] 2011 IOM cites ACOG informational brochures for its benign judgment on the "side effects" of hormonal contraceptives (2011 IOM at 105,135), neglecting to mention that these brochures additionally contain discussions of the "risks" of oral contraceptives, including, as outlined above, heart attacks, strokes, blood clots, and liver tumors.

[36] 2011 IOM at 105-06.

[37] *See, e.g.*, Heffron, *supra*, which states: "Funding: US National Institutes of Health and the Bill & Melinda Gates Foundation."

[38] 2011 IOM at 107.

For the year 2013, the expected incidence of cancers of the breast, liver and cervix among American females will surpass the incidence of cancers of the colon, endometrium and cervix by 193,050 cases. The total number of invasive and *in situ* breast cancers are expected to reach 296,980 cases.[39] Cancers of the liver and cervix will reach 20,260 total cases. Together, the cancers that combined oral contraceptives cause will total 317,240 cases.

By contrast, the cancers that oral contraceptives are known to prevent (endometrial and ovarian) are expected to total 71,800. If the disputed protective effect of oral contraceptives on colon cancer risk is included, then the total number of expected cancers that oral contraceptives prevent would climb to 124,190 cases.[40]

Similarly, mortality rates for the cancers that combined oral contraceptives cause (breast, liver and cervix) far exceed the mortality rates that oral contraceptives are known to prevent (endometrial and ovarian) by 28,210 deaths. If the disputed protective effect of oral contraceptives on colon cancer is included,

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[39] The expected number of invasive breast cancers for American females is 232,340. The expected number of in situ (early) breast cancers is 64,640. In situ breast cancers are reported in small print at the bottom of page 4 in the document, "Estimated number of new cancer cases and deaths by sex, US, 2013." *Cancer Facts and Figures 2013*, American Cancer Society, available at: http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-036845.pdf (last visited April 29, 2013).

[40] *Id.* at 4.

then the mortality rates for the cancers that combined oral contraceptives cause still exceed the mortality rates for cancers that oral contraceptives allegedly prevent by 3,680 deaths.

The Government's amici in other HHS cases have also been favorably quoting a 2005 report from the UN/UNFPA/WHO/World Bank[41] which pre-dates the findings from both the *Mayo Clinic Proceedings* meta-analysis in 2006

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[41] "Several WHO committees work on creating evidence-based family planning guidelines and on keeping them up-to-date on a continuous basis. They regularly review the safety of COCs (combined oral contraceptives) and assess the balance of risks and benefits of COC use and they have determined that for most healthy women, the health benefits clearly exceed the health risks." UNDP/UNFPA/WHO/World Bank Special Programme of Research, Dev. & Research Training in Human Reprod. (HRP), *Carcinogenicity of Combined Hormonal Contraceptives and Combined Menopausal Treatment* 1 (2005).

This statement ignores an important warning issued by the International Agency for Research on Cancer Working Group when it published the following in a 2005 issue of the journal, *Lancet Oncology*:

Because use of combined contraceptives heightens the risk of some cancers and reduces that of others, it is possible that the overall net public-health outcome could be beneficial, **but a rigorous analysis is needed to show this**. Such an analysis is outside the scope of an IARC monograph meeting and would include quantitative estimates of the age-specific absolute risk at each cancer site, the availability and effectiveness of cancer screening, the availability, effectiveness, and side-effects of cancer treatments, and other health and societal effects, both beneficial and adverse. **Since these factors vary throughout the world, the risk-benefit analysis should be specific to each country and population.**

Cogliano V, Grosse Y, Baan R, Straif K, Secretan B, El Ghissassi F. *Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment*. Lancet Oncology 6:552-553 (2005)(emphasis added).

discussed above and the findings from at least two studies that strongly link use of oral contraceptives with the aggressive, deadly triple-negative breast cancer reported in the studies: Ma et al. 2010 and Dolle et al. 2009. The Dolle et al. 2009 study reports a statistically 6.4-fold increased risk of triple-negative breast cancer for women who started taking oral contraceptives before age eighteen. The authors wrote, "Triple-negative breast cancer constitutes a clinically challenging type of breast cancer that occurs more frequently in younger women (under age 50) and African-American women and is associated with significant aggressiveness as compared with other subtypes."[42]

The Ma et al. 2010 study reported a 2.9-fold increased risk for triple negative tumors among older women (ages 45–64 years) who started using oral contraceptives before age 18.[43]

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[42] Dolle J, Daling J, White E, Brinton L, Doody D, et al. *Risk factors for triple-negative breast cancer in women under the age of 45 years*. Cancer Epidemiol Biomarkers Prev 18(4)1157-1166 (2009).

[43] Ma H, Wang Y, Sullivan-Halley J, Weiss L, Marchbanks PA, Spirtas R, Ursin G, Burkman RT, Simon MS, Malone KE, Strom BL, McDonald JA, Press MF, Bernstein L. *Use of four biomarkers to evaluate the risk of breast cancer subtypes in the Women's Contraceptive and Reproductive Experiences Study*. Cancer Research 70(2):575-587 (2010), available at http://cancerres.aacrjournals.org/content/70/2/575.long (last visited April 29, 2013).

- **The IOM Report Ignored the Increased Risks to Teenagers**

As discussed above, a 2009 study showed an alarming 3.2-fold increased risk of triple negative breast cancer, the most difficult and deadly form of breast cancer to treat, in women taking oral contraceptives. Not only did the IOM report fail to cite or balance the results of this study, but it also failed to reveal that the same 2009 study showed an even more alarming 6.4-fold increased risk of the deadly triple-negative breast cancer in teenagers who started taking oral contraceptives before age eighteen.[44]

The IOM Report wholly fails to account for the fact that teenagers are the least likely group to be aware of the health risks associated with use of hormonal steroids such as oral contraceptives and Depo-Provera, and the least likely to know the medical history of extended family members. The most cancer-susceptible time in a woman's life takes place between the onset of menstruation and first full term pregnancy (known as the "susceptibility window").[45] That is the period when the breasts are growing and nearly all of the breast lobules consist of immature,

[44] J. Dolle et al., n. 15, *supra.*

[45] J. Russo and H. Russo, *Development of the Human Mammary Gland*," in The Mammary Gland, eds. M. Neville and C. Daniel (New York: Plenum Publishing Corporation, 1987).

cancer-susceptible Type 1 and 2 lobules where 95% of all cancers are known to start.

However, by the end of a first full term pregnancy, 85% of the breast lobules are fully mature and permanently cancer-resistant. Genetic changes that take place in the breast lobules during a full term pregnancy provide lifelong protection against breast cancer.[46] [47] [48] [49] [50] The worst time in a woman's life to be exposed to a carcinogen is during the "susceptibility window."

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[46] Jose Russo, Gabriela A. Balogh, Irma H. Russo, and the Fox Chase Cancer Center Hospital Network Participants, *"Full-Term Pregnancy Induces a Specific Genomic Signature in the Human Breast,"* Cancer Epidemiology, Biomarkers and Prevention 17, no. 1:51-66 (January 2008).

[47] I. Verlinden, N. Güngör, K. Wouters, J. Janssens, J. Raus, and L. Michiels, *"Parity-Induced Changes in Global Gene Expression in the Human Mammary Gland,"* European Journal of Cancer Prevention 14:129-137 (2005).

[48] Medical texts and medical authorities agree that delayed first full term pregnancy is a risk factor for breast cancer. Every one year delay of a first full term pregnancy increases the risk of premenopausal breast cancer by 5% and postmenopausal breast cancer by 3%. Françoise Clavel-Chapelon and Mariette Gerber, *"Reproductive Factors and Breast Cancer Risk,"* Breast Cancer Research and Treatment 72, no. 2:107-115 (2002).

[49] In a landmark study, Harvard scientists reported that women who had a first full term pregnancy at age 35 in comparison with those who had a first full term pregnancy at age 17 had a three-fold greater risk of breast cancer. MacMahon, B, Cole P, Lin TM, Lowe CR, Mirra AP, Ravnihar B, Salber EJ, Valaoras VG, Yuasa S. *Age at First Birth and Breast Cancer Risk*. Bull WHO 43:209-221 (1970).

[50] "Indeed, if women had larger family sizes and longer lifetime durations of breastfeeding that were typical of developing countries until recently, the cumulative incidence of breast cancer in developed countries is estimated to be reduced by more than half (from 6.3 to 2.7 per 100 women) by age 70 years." Beral V, et al. Breast cancer and breastfeeding: collaborative re-analysis of

Indeed, a 2006 meta-analysis of studies on oral contraceptives and breast cancer risk published in the journal, *Mayo Clinic Proceedings,* reported that "[t]he association between [oral contraceptive] use and breast cancer risk was greatest for parous women who used OCs [oral contraceptives] 4 or more years before FFTP [first full term pregnancy]."[51] The authors reported a statistically significant 52% risk elevation for this group.

They also found a statistically significant 44% increased risk of pre-menopausal breast cancer among women who started using oral contraceptives before first full term pregnancy. They explained the biological rationale as follows:

> The results of prior studies and of ours are consistent with the hypothesis that OCs (oral contraceptives) can be carcinogenic, especially when used before FFTP (first full term pregnancy). The nulliparous (non-childbearing) breast is composed of undifferentiated structures, and it is only during a full-term pregnancy that the breast attains its maximum development. **This** development occurs in 2 distinct phases, an early growth phase and a late phase of lobular differentiation. The undifferentiated breast structures found in the nulliparous breast may be more susceptible to carcinogens than the more differentiated structures found in the fully developed breast. For example, in Hiroshima and Nagasaki, Japan, nulliparous women who

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individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease. *Lancet* 2002;360:187-195.

[51] Kahlenborn C, Modugno F. Potter DM, Severs WB. *Oral contraceptive use as a risk factor for premenopausal breast cancer: A meta-analysis*. Mayo Clinic Proceedings 2006;81(10):1290-1302. Abstract available at http://www.ncbi.nlm.nih.gov/pubmed/17036554 (last checked April 29,2013).

> were exposed to radiation from the atomic bomb developed breast cancer far more frequently than women who had already borne children at the time of exposure.[52]

In sum, the Government completely ignored the mandated drugs' many serious health risks as well as ignoring the established ties between hormonal contraceptives to the cancer epidemic among young healthy women to whom carcinogenic drugs are given to prevent fertility (which is not a disease) or even for reasons that can be as benign as prevention of acne. Because the mandated drugs significantly increase risks breast, liver and cervical cancer in addition to stroke, HIV and a host of serious diseases, the Government simply cannot meet the RFRA requirement that the HHS Mandate "furthers" an asserted governmental interest in promoting women's health.[53]

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[52] *Id.* at 1297.

[53] In addition to the Government's not having met its burden under RFRA, the failure of the IOM report to consider or even balance the putative benefits with the increased health risks reveals that the Mandate is "arbitrary and capricious" under the Administrative Procedures Act (APA). The judicial standard for review under the APA "arbitrary and capricious" standard provides, "An agency rule would be arbitrary and capricious if the agency . . . **entirely failed to consider an important aspect of the problem**, . . . *Motor Vehicle Mfrs. Ass'n of U.S., Inc. v. State Farm Mut. Auto Ins. Co*., 463 U.S. 29, 43 (1983) (emphasis added). Here, the HHS Mandate is arbitrary and capricious by virtue of the fact that the Government "entirely failed to consider" that the mandated drugs *increase* risk of disease rather than prevent disease.

CONCLUSION

For the foregoing reasons, Amici request that this Court reverse the decision of the district court denying Plaintiffs' motion for a preliminary injunction and remand this case to the district court with instructions to enter a preliminary injunction as requested by Plaintiffs.

Respectfully submitted this 7th day of May, 2013,

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1. This brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because it contains **5,623** words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii).

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DATED: May 7, 2013

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CERTIFICATE OF SERVICE

I certify that on May 7, 2013, I electronically filed the foregoing with the Clerk of the Court for the United States Court of Appeals for the District of Columbia Circuit by using the CM/ECF system. I certify that all registered participants in the case will receive service by the CM/ECF system.

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