



November 18, 2019

Admiral Brett Giroir, Acting Commissioner
Food and Drug Administration

and

Steven Tave, Director
Office of Dietary Supplement Programs

and

Janet Woodcock, Director
Center for Drug Evaluation and Research

Food and Drug Administration
10001 New Hampshire Ave
Hillandale Bldg., 4th Floor
Silver Spring, MD 20993

and

10903 New Hampshire Ave
Silver Spring, MD 20993

Dear Acting Commissioner Giroir and Directors Tave and Woodcock:

This letter provides the Food and Drug Administration (FDA) with disturbing findings from our investigation into dietary supplements that explicitly or implicitly claim to treat female infertility.¹ We urge the FDA to pursue enforcement action against the 39 products we identify as being marketed as unapproved and/or misbranded drugs under the Food, Drug, and Cosmetic Act (FDCA) by issuing warning letters to the offending companies and prohibiting their sale.

Manufacturers of these 39 fertility supplements were unable to provide us, upon our request, with scientific substantiation of their products' claims regarding female fertility. Accordingly, we are also sending a letter to the Federal Trade Commission (FTC), urging that it act alongside the FDA to pursue legal actions against these manufacturers on the grounds that these products are misbranded under the FTC Act.

Products marketed to treat infertility are considered drugs under the FDCA and may only be legally marketed if FDA approved.² This category of supplements is worthy of the FDA's urgent attention because women seeking to become pregnant are particularly vulnerable to exploitation. In the U.S., approximately 12 couples in 100 have trouble becoming pregnant, and about ten in 100 (6.1 million) women of childbearing age face difficulties becoming or staying pregnant, according to the Centers for Disease Control and Prevention.³ Women may be under time pressure to conceive, and relying on ineffective supplements, rather than seeking effective, proven treatments, may waste precious time. Many women are willing to go to great lengths to overcome the emotional and physical struggle of being unable to get pregnant, and these purported fertility aids seek to profit from the vulnerability created by this sense of urgency.

I. *Identification of Products Marketed as Unapproved Fertility Drugs*

We conducted a market scan and compiled a list of dietary supplements for women that claimed, directly or by implication, to help with infertility. We searched each manufacturer's website or Amazon product page for valid scientific studies to support their claims. When none were found, we reached out to the company to ask for scientific substantiation. Transcripts of those interactions are included in the Appendix.

We identified 39 women's fertility supplements, containing a total of 94 ingredients, manufactured by 27 companies that were unable to substantiate their products' claims.⁴ These findings show that health fraud and unapproved drug claims are rampant in the female fertility supplement marketplace.

As detailed in the attached chart, the manufacturers of these 39 female fertility supplements claim that their products treat infertility, targeting women who may have had difficulties conceiving or who may have underlying health conditions that put them at risk of infertility, such as Polycystic Ovary Syndrome (PCOS), obesity, or diabetes. Their claims include such statements as:

- "Recommended for all trying-to-conceive women, and particularly women trying to conceive later in life & women with PCOS." (Ovaboost)
- "Especially recommended for: Women with PCOS and/or obesity, Women with infertility (Conflam-Forte)
- "[T]reatment of choice for many fertility-related issues. D-Chiro-Inositol helps to lower elevated blood insulin levels, which more and more research is showing to be the cause of PCOS." (D-Chiro Inositol)
- "More than 800 customers shared their experience with us in a self-reported, opt-in internet survey... 1 in Every 3 Survey Participants Diagnosed with Unexplained Infertility Became Pregnant While Using FertilAid for Women" (FertilAid for Women)
- "[F]ormulated for women who may be having difficulty conceiving" (Pregnitude)
- "Proxceed Women is recommended for women of reproductive age who: are experiencing fertility problems [...] are preparing for IVF and want to ensure the best possible quality of egg (ovum) and an optimum environment for implantation"
- "[T]he ingredients in our herbal blend have been used for centuries in TCM and Ayurvedic Medicine to overcome fertility issues" (Women's Fertility Boost)

Some manufacturers make claims that could deter patients from seeking effective, FDA-approved drugs because they indicate that the supplements are effective alternatives to conventional care. Some such claims even deride FDA-approved fertility treatments as invasive, expensive, or ineffective, further discouraging women from using these options:

- "[A] perfect natural alternative to fertility drugs or invasive treatments." (FertilHerb for Women)

- “PHYSICIAN FORMULATED: At Doctor MK's we know that PCOS can be stressful. Our goal is to help women overcome infertility and increase pregnancy rates without the unwanted side effects of prescription medications.” (doctorMK's Natural Myo-inositol)
- “[R]ecognized as a viable non-prescription option for women who may be having difficulty conceiving.” (Pregnitude)
- “If you are tired of fertility drugs and their lame promises, we have news for you!” (Conceive Plus Women's Fertility Support)
- “I've been taking it for 8 days now and i'm (sic) getting amazing readings on my ovacue monitor. This is better than when I took clomid!” (testimonial for FertileDetox)
- “No need to fuss with making a tea or having to pay thousands for drugs and other treatment methods that can cause side effects” (Ready. Set. Go!)

The manufacturers also make other types of claims that indicate the product is being marketed as a drug according to FDA guidance.⁵ Some products include a significant or recognizable portion of the word “(in)fertility” in their name (*e.g.*, FertilAid). Some product websites cite disease-related research publications. And some manufacturers otherwise employ scientific or medical terminology suggesting their products affect a characteristic sign or symptom of infertility, making claims like:

- “Mega-dose, pharmaceutical-grade CoQ 10 for healthy eggs... OVOENERGEN™ was developed in collaboration with physicians at Center for Human Reproduction, a leading IVF center focused on egg development, antioxidants and women's fertility. CHR endorses and recommends OVOENERGEN™ CoQ10.”
- “Indications: Fertility, Hormone Balance, Ovarian Function, Reproductive Health” (Pregnositol)
- “Regular ovulation is promoted with Chaste tree berry and Tribulus. Tribulus has research supporting this function and shows better results for women who took it with the ovulation-stimulating hormonal drug” (Pregnancy Prep)
- “Studies indicate that preconception multivitamin supplementation *in and of itself* may enhance fertility and increase your chances of conception” (FertilAid for Women)
- “[M]ounting scientific evidence [is] linking toxin exposure to decreases in male and female fertility as well as increases in pregnancy complications and birth defects. FertileDetox™ for Men and Women is designed to improve fertility and promote the health of a baby by helping with efficient elimination of environmental toxins from the body.”

II. *These Unapproved Drugs Should Be an Enforcement Priority for FDA*

While marketing of unapproved drugs is illegal under any circumstances, the marketing of these products presents particular risks warranting FDA enforcement action under the agency's principles for enforcement priorities.⁶ Of FDA's six established enforcement priorities, at least three apply here:

1. Drugs that lack evidence of effectiveness;
2. Drugs that present direct challenges to the new drug approval and OTC drug monograph systems inasmuch as they are "unapproved drugs that directly compete with an approved drug;" and
3. Health fraud drugs.

As we detail below, the infertility treatments described in this letter each meet one or more of these three criteria.

1) The drugs lack evidence of effectiveness

The manufacturers of these 39 fertility supplements failed to provide scientific substantiation of their products' claims regarding female fertility. Of the websites for the 39 supplements:

- 30 websites cited no studies at all;
- 4 cited studies that showed no increase in rates of pregnancy;
- 4 cited studies that did not look at rates of pregnancy; and
- 1 cited a study that only assessed the ingredient using a dose that was eight times the dose contained in the supplement.

The Appendix contains a more detailed summary with product names.

We also contacted all 27 manufacturers of the 39 supplements and asked for evidence that their products increase the likelihood of pregnancy. Of the 39 emails we sent to these companies:

- 11 received no response;
- 16 responses cited no studies at all;
- 4 responses cited customer reviews as evidence that the supplements increased pregnancy rates;
- 4 responses cited studies that did not look at rates of pregnancy;
- 3 responses cited studies that showed no increase in rates of pregnancy; and
- 1 response cited a study with no control group.

One particularly egregious misrepresentation was made by Fairhaven Health of Bellingham, Washington, which sells eight fertility supplements. Fairhaven's website for FertilAid for Women says: "One Clinical Trial Reported that 12 of 16 Previously Infertile Women Were Able to Get Pregnant after Supplementing with PABA over Several Months."⁷ We

found that this was a 77-year-old uncontrolled study in *men*, not women.⁸

Another manufacturer, after acknowledging to us in an email exchange that it lacked evidence for its product, expressed skepticism about the category, stating: “I think you’ll be hard pressed to find any supplement company that can definitively say that their product increases the chances of becoming pregnant. If you do, I’d be very curious to see.”⁹

2) *The drugs directly compete with an FDA-approved drug.*

FDA has approved several oral and injectable drugs to support fertility, and unapproved drugs marketed as dietary supplements can compete with these products without having undergone the safety and efficacy review required of their FDA-approved counterparts. FDA-approved drugs indicated to treat infertility include clomiphene, clomiphene citrate, letrozole, gonadotropins, human chorionic gonadotropin, bromocriptine, and cabergoline.¹⁰ Alarming, many of the supplements in this letter go well beyond the technical indications of these approved drugs, in that they frequently claim actual fertility and/or pregnancy benefits.

In short, these female fertility supplements are unapproved drugs that compete with these FDA-approved drugs, thereby potentially persuading some women to delay or forgo safe and effective medical treatment.

3) *The drugs are health fraud products.*

FDA defines health fraud products as those “represented as being effective to diagnose, prevent, cure, treat, or mitigate disease (or other conditions), or provide a beneficial effect on health, but which have not been scientifically proven safe and effective for such purposes.”¹¹ A health fraud product presents an indirect health hazard if “as a result of reliance on the product, the consumer is likely to delay or discontinue appropriate medical treatment.”¹²

Fertility supplements are health fraud products presenting “indirect health hazards,” as defined by FDA,¹³ because they claim to treat infertility despite lack of evidence of effectiveness at increasing the chances of pregnancy, and they may lead women to delay or discontinue effective treatments such as FDA-approved drugs or assisted reproductive technology (ART).

The fertility supplements identified in this letter also warrant enforcement prioritization as indirect health hazards based on the criteria for evaluating regulatory actions against such products described in the FDA’s Health Fraud Compliance Policy Guide.¹⁴ As stated in the guide, the agency will consider several criteria in determining whether to take enforcement action, including three that are met in this case:

- “Whether the therapeutic claims or conditions to be treated are significant as interpreted by the appropriate center;”
- “Whether there are scientific data or specific information to support the safety or effectiveness of the product for its intended or customary use;” and
- “The degree of vulnerability of the prospective user group, *e.g.*, the elderly, persons with illnesses for which there is no recognized effective treatment.”

All three conditions are met here. First, the products we identify claim to treat a condition that is significant and highly prevalent, as there are more than six million women in the U.S. ages 15-44 who experience difficulty in becoming pregnant or staying pregnant.¹⁵ Second, as illustrated above, the scientific data that manufacturers rely upon to support the efficacy of these products is weak. Finally, the product targets a vulnerable population because, as noted above, women may be under time pressure to conceive, and may rely on ineffective supplements rather than seeking effective, proven treatments, wasting precious time.

Action Requested

We respectfully urge FDA to immediately issue warning letters and bring other enforcement actions to require cessation of sales of these fertility supplements, as well as other such products, and to allow inspectors to seize the products.

We appreciate past FDA actions in response to CSPI letters regarding dietary supplements, including the January 2018 response to our letter¹⁶ on drugs marketed for treatment of opioid addiction, as well as FDA's more recent actions involving drugs that claim to prevent, treat, or cure neurological diseases/health conditions and products claiming to be tobacco cessation aids highlighted by our April 2019 letter.¹⁷

We would welcome the opportunity to speak with you at your convenience regarding our urgent and mutual interest in eliminating false and deceptive advertisements for harmful dietary supplements. We seek to ensure that Americans' access to truly effective treatments is not hampered by the misleading marketing of supplements, including those for female fertility.

Sincerely,

Peter Lurie, M.P.H., M.D.
President and Executive Director
Center for Science in the Public Interest

Laura MacCleery
Policy Director
Center for Science in the Public Interest

Notes

¹ Fertility is defined as “being able to become pregnant (conceive)” (U.S. Department of Health and Human Services. *Female Infertility: Quick Facts*. 2019. <https://www.hhs.gov/opa/reproductive-health/fact-sheets/female-infertility/index.html>. Accessed August 27, 2019).

² See, e.g. U.S. Food and Drug Administration. *Warning Letter: Celloxess LLC*. July 22, 2016. <https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/celloxess-llc-07222016>. Accessed August 27, 2019.

³ Fertility is defined as “being able to become pregnant (conceive)” (U.S. Department of Health and Human Services. *Female Infertility: Quick Facts*. 2019. <https://www.hhs.gov/opa/reproductive-health/fact-sheets/female-infertility/index.html>. Accessed August 27, 2019).

⁴ These products were still available on Amazon as of August 2019.

⁵ U.S. Food and Drug Administration. Small Entity Compliance Guide on Structure/Function Claims. January 2002. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/small-entity-compliance-guide-structurefunction-claims>

⁶ U.S. Food and Drug Administration. *Market Unapproved Drugs- Compliance Policy Guide*. 2011; Sec 440.100. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ marketed-unapproved-drugs-compliance-policy-guide>. Accessed July 25, 2019.

⁷ Fairhaven Health. Product listing: FertilAid for Women. <https://www.amazon.com/Fairhaven-Health-fertilaid-for-women-FertilAid-Women/dp/B0002G2M9Y>. Accessed September 11, 2019.

⁸ Sieve BF. The clinical effects of a new B-complex factor, para-aminobenzoic acid, on pigmentation and fertility. *South Med Surg*. 1942; 104: 135–139.

⁹ From email correspondence with Fertility Support for Her, January 28, 2019.

¹⁰ National Institutes of Health. *Fertility Treatments for Females*. January 31, 2017. <https://www.nichd.nih.gov/health/topics/infertility/conditioninfo/treatments/treatments-women>. Accessed August 27, 2019.

¹¹ U.S. Food and Drug Administration. *Marketed Unapproved Drugs- Compliance Policy Guide*; Sec. 120.500. September 19, 2011. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ marketed-unapproved-drugs-compliance-policy-guide>. Accessed July 25, 2019.

¹² *Id.*

¹³ U.S. Food and Drug Administration. *Health Fraud- Factors in Considering Regulatory Action*; Sec 120.500. March 1995. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/cpg-sec-120500-health-fraud-factors-considering-regulatory-action> . Accessed September 12, 2019.

¹⁴ *Id.*

¹⁵ U.S. Department of Health and Human Services. *Female Infertility: Quick Facts*. 2019. <https://www.hhs.gov/opa/reproductive-health/fact-sheets/female-infertility/index.html>. Accessed July 25, 2019.

¹⁶ Letter from U.S. Food and Drug Administration to CSPI. January 24, 2018. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ marketed-unapproved-drugs-compliance-policy-guide>

¹⁷ CSPI. FDA Urged to Take Enforcement Action against Manufacturers of Dietary Supplements that Promise to Help Smokers Quit. April 23, 2019. <https://cspinet.org/news/fda-letter-dietary-supplements-smoking-cessation>