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CITIZEN PETITION

The undersigned submits this petition under 21 C.F.R. § 10.30 to request the Commissioner of the Food and Drug Administration (“FDA”) to revise the FDA’s guidance document entitled “Labeling for Combined Oral Contraceptives” (“COC Guidance”)¹ so that the labels of combined oral contraceptives (“COCs”) have warnings relating to the risk of thromboembolic disease that are consistent with those required by the European Medicines Agency (“EMA”).

¹ Center for Drug Evaluation and Research, FDA, Guidance for Industry: Labeling for Combined Oral Contraceptives (Rev. 1 Mar. 2004).

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A. Action requested

Petitioner requests that FDA revise the draft COC Guidance by deleting the existing recommended warning that the risk of thromboembolic disease is unrelated to duration of use and adopt the EMEA warning that the risk is highest in the first year and declines with time. Specifically, petitioner recommends deletion of the current warning recommended by FDA that relates to duration of use and that it be replaced with: "There is an excess risk of thromboembolic disease during the first year a woman uses a combined oral contraceptive."

B. Statement of grounds

In March 2004, FDA issued revision 1 to its draft COC Guidance. Although the COC Guidance is identified as a draft, it describes FDA's recommendations for the labeling of COCs to be provided to health care providers and patients. Like other "draft" guidances and notwithstanding FDA's standard disclaimers, FDA expects industry to comply. As anticipated by FDA, manufacturers of COCs comply with FDA's guidance, which ensures that warnings that FDA believes are appropriate for the safe and effective use of COCs are consistently provided by all manufacturers.

The COC Guidance recommends specific warnings relating to vascular risks. FDA specifically advises that COC labeling contain the following statement in the "WARNINGS" section under item 1(b) "Thromboembolism," "The risk of thromboembolic disease associated with [COCs] is not related to length of use and disappears after the use of the drug product is stopped."² The sentence cites a 1981 article by Bruce Stadel entitled "Oral Contraceptives and Cardiovascular Disease (First of Two Parts)" for support.³

The cited Stadel article is a review of published literature and does not contain any original data. There is a single sentence in the article that supports the warning required by the COC Guidance. This sentence, which can be found on pages 613 and 614, states: "Epidemiologic research has found that the risk of overt venous thromboembolic disease increases during the first month of oral-contraceptive use, and then remains constant regardless of the duration of use, although few data on continuous use for more than three

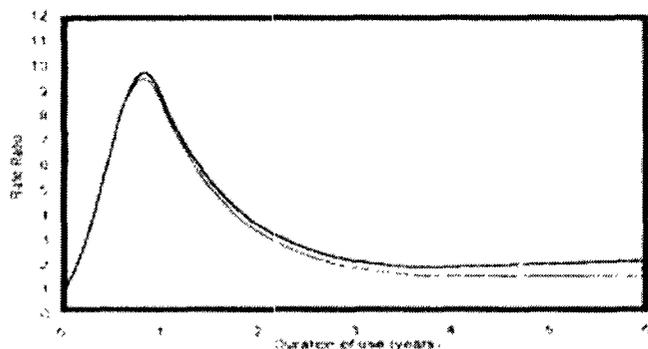
² Id. at 4-5.

³ Bruce V. Stadel, Oral Contraceptives and Cardiovascular Disease (First of Two Parts), 305 N. Eng. J. Med. 612 (1981) (Exhibit 1).

years are available.”⁴ The two references cited in support of this proposition are an article by Sartwell et al. published in 1969 in the American Journal of Epidemiology⁵ and a 1973 article by the Boston Collaborative Drug Surveillance Programme that appeared in the Lancet.⁶ These articles contained retrospective studies of oral contraceptives that were in use in the 1960s and early 1970s that were generally of a higher estrogen dosage than more current COCs.

These early case-controlled studies are inconsistent with the results of more recent case controlled studies in which the patients whose medical records were reviewed used COCs with lower estrogen doses and in some cases different progestogens.

In one study published in 1997, Suissa and colleagues reanalyzed data from the Transnational case-control study and determined that in first time users of COCs the adjusted risk profile increases rapidly, peaks after one year of use, and then decreases and stabilizes at around two years of use for both second and third generation COCs.⁷ See Figure 1 below.



⁴ Id. at 613-14 (emphasis added) (citations omitted).

⁵ PE Sartwell et al., Thromboembolism and Oral Contraceptives: an Epidemiologic Case-Control Study, 90 Am. J. Epidemiology 365 (1969).

⁶ Oral Contraceptives and Venous Thromboembolic Disease, Surgically Confirmed Gallbladder Disease, and Breast Tumors: Report from the Boston Collaborative Drug Surveillance Programme, 1 Lancet 1399 (1973).

⁷ Samy Suissa et al., First-Time Use of Newer Oral Contraceptives and the Risk of Venous Thromboembolism, 56 Contraception 141 (1997) (Exhibit 2).

Figure 1. Adjusted rate ratio of venous thromboembolism as a function of duration of second generation (thin line) and third generation (thick line) oral contraceptive use among first-time users compared with nonusers. Rate ratio, adjusted for linear age, smoking, alcohol use, study center, and body mass index, fitted by quadratic splines using logistic regression.⁸

In 2002, Lidegaard et al. reported the results from a five-year case-controlled study involving women ages 15-44 years old who suffered a first ever deep vein thrombosis or pulmonary embolus in any Danish hospital from the beginning of 1994 to the end of 1998.⁹ The crude aged matched odds ratio decreased with length of COC use. See Table 1 below.

Table 1
Risk of venous thromboembolism in users of different types of [COCs]

Duration of use (years)	Case/Control	Crude* OR	Crude* 95% CI
<1	124/173	7.0	5.2 - 9.3
1-5	137/412	3.3	2.6 - 4.3
>5	229/596	2.8	2.3 - 3.4

* Crude OR: Matched by 1 year age groups and year.

In 2004, the results of a case-controlled study among women who were members of the Kaiser Permanente Medical Care Program in California were published.¹⁰ The authors concluded that “the risk of [venous thromboembolism] was highest in the first year of [COC] use and diminished with increasing duration of use.”¹¹ See Table 2 below.

Table 2

⁸ Id. at 144.

⁹ Øjvind Lidegaard et al., Oral Contraceptives and Venous Thromboembolism: a Five Year National Case-Control Study, 65 *Contraception* 187 (2002) (Exhibit 3).

¹⁰ Stephen Sidney et al., Venous Thromboembolic Disease in Users of Low-Estrogen Combined Estrogen-Progestin Oral Contraceptives, 70 *Contraception* 3 (2004) (Exhibit 4).

¹¹ Id. at 8.

Results of multivariate analysis according to [COC] use

Duration of current use (months)	OR Model*	95% CI Model*
<12	5.43	2.12–13.94
12 – 59	5.73	2.98–10.99
≥60	3.12	1.99–4.88

* Adjusted for age, race/ethnicity, income and BMI.¹²

These and other studies bring into question the adequacy of the warning relating to the risk of thromboembolic disease and duration of use of the COC that is recommended by FDA. The current warning is based on historical information on products with different dosages and is not reflective of more recent data generated by various independent groups. Further, this warning is inconsistent with the findings and recommendations of EMEA, which in 2001 concluded that “[t]here is an excess risk of [venous thromboembolism] during the first year a woman ever uses any COC.”¹³

As a result of this discrepancy in recommendations, manufacturers of COCs that distribute COCs in Europe as well as the United States are required to have different and inconsistent warnings in order to comply with the recommendations of the controlling regulatory authority.

No individual company can resolve the inconsistent positions taken by the FDA and the EMEA. Although FDA regulations (21 C.F.R. § 314.70(c)) permit the holder of an approved new drug application to submit a “Changes Being Effected” supplement to add or strengthen a warning, that option is not available in this situation. If language is added to the labeling that warns that the greatest risk of thromboembolic disease associated with COC use occurs in the first year, it will either contradict and, therefore, weaken the existing warning that the risk of thromboembolic disease is unrelated to duration of use or cause both warnings to appear nonsensical. In either case, FDA approval is required.

C. Environmental impact

¹² Id. at 7.

¹³ EMEA Committee for Proprietary Medicinal Products, EMEA, CPMP Public Assessment Report: Combined Oral Contraceptives and Venous Thromboembolism 3 (Sept. 28, 2001) (EMEA Doc. Ref: EMEA/CPMP/2201/01/en/Final) (Exhibit 5).

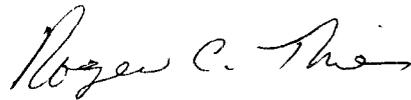
The actions requested in this petition are categorically exempt from the requirement of an environmental impact statement or an environmental assessment pursuant to 21 C.F.R. § 25.30(h).

D. Economic impact

Pursuant to 21 C.F.R. § 10.30(b), economic impact information will be submitted if requested.

E. Certification

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner that are unfavorable to the petition.



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Attachments