

## Comments on Labeling for Combined Oral Contraceptives

Docket No. 2000D-1350

Thank you for the opportunity to comment on the draft labeling for combined oral contraceptives (COCs). Family Health International (FHI) is a nonprofit public health organization that works to improve access to safe, effective, and affordable family planning. We also work to translate health information into programs that influence individual behavior and improve community health. We appreciate all the work the FDA has put into this labeling, and the language is more readable than earlier versions. However, we have some areas of concern.

Foremost, the standards the FDA has used for acceptance of scientific literature appear unbalanced. For example, older studies relating to high-dose pills have been cited to support hazards of today's low-dose pills. In contrast, older studies relating to high-dose pills have been excluded to support the non-contraceptive benefits of low-dose pills. This is internally inconsistent, and potentially misleading. The same inclusion criteria for evidence must be used for both risks and benefits. The draft label needs updated references and better scientific balance. Although randomized trial data is not available for all aspects of COC effectiveness and safety, the best data are still obtained from well-conducted thorough systematic reviews. We have reviewed this literature systematically and extensively as part of Cochrane Collaboration reviews and collaboration with the World Health Organization's (WHO's) program on Medical Eligibility Criteria (MEC) for contraceptive use. We would be happy to share these reviews (some of which are not yet published) with the FDA, and would appreciate the opportunity to further assist the FDA in ensuring that this new labeling is accurate, comprehensive, and understandable.

### A. Provider label

1. Effectiveness: The best data on effectiveness of contraceptive methods come from James Trussell. The current amalgam presented in FDA's draft labeling is potentially misleading. First, this table appears to be based only on selected data (that submitted to the FDA) rather than the totality of the literature. Second, the differences in effectiveness between COCs and barrier methods appear exaggerated, and third, many modern contraceptive methods are not included.
2. Contraindications: The best data on the safety and eligibility criteria for COCs come from the WHO MEC for contraceptive use. These consensus recommendations from an international group of contraceptive experts based on systematic reviews were recently revised in 2004. Summary tables are available at [http://www.who.int/reproductive-health/publications/MEC\\_3/index.htm](http://www.who.int/reproductive-health/publications/MEC_3/index.htm). In the MEC, conditions rated "4 (condition which represents an unacceptable health risk if the contraceptive method is used)" should be considered absolute contraindications to the use of a method, while conditions rated "3 (condition where the theoretical or proven risks usually outweigh the advantages of using the method)" should be considered relative contraindications. We recommend that the FDA base recommendations on who can and cannot use COCs on the WHO guidance throughout the labeling. For example, the "undiagnosed abnormal genital bleeding" contraindication should be deleted both because of vagueness and clinical irrelevance. Most abnormal menstrual bleeding in young women has a hormonal etiology, does not warrant a biopsy to establish a diagnosis, and oral

contraceptives are a treatment of choice. If this contraindication is to be retained, it should be changed to “clinical suspicion of endometrial cancer” or something equivalent.

3. Warnings: We analyzed the publication date of the 74 references cited. The median publication date was 1982 and the mode, 1986. Thus, most references cited are very old. Key recent references are missing, suggesting that a systematic review for recent publications has not been done. For example, older data on cardiovascular complications showed a much greater risk with COC use than newer data (WHO Technical Report Series 877. Cardiovascular disease and steroid hormone contraception. Geneva, World Health Organization, 1998). With regard to hepatic neoplasms, recent population-based information from three continents refuting alleged increased risks of hepatocellular carcinoma with oral contraceptives is missing (Waetjen et al. *Obstet Gynecol* 1996;88:945). Instead, flawed case-control studies continue to make this claim, which now appears untenable.
4. Precautions: No data support the need for annual pelvic examination, cervical cytology, or laboratory testing (Stewart et al. *JAMA*. 2001;285:2232). Only blood pressure screening is recommended by WHO ([http://www.who.int/reproductive-health/publications/rhr\\_02\\_7/rhr\\_02\\_07\\_q20.html](http://www.who.int/reproductive-health/publications/rhr_02_7/rhr_02_07_q20.html)).
5. Drug interactions: the data regarding drug interactions is also based on a single old reference. There have been several new well-done systematic reviews of COC use with antibiotics (Archer et al. *J Am Acad Dermatol*. 2002;46:917, Dickinson et al, *Obstet Gynecol*. 2001;98:853). This topic was also recently reviewed by WHO. Furthermore, information on HIV treatments is incomplete. Specifically, non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as nevirapine, efavirenz, and delavirdine, are metabolized by CYP3A4 and also inhibit or induce this enzyme, resulting in increases or decreases in the concentration of concomitantly administered COCs.
6. Nursing mothers: For nursing mothers who are  $\geq 6$  months postpartum, COCs may be used (WHO MEC). Additionally, even for women who are more recently postpartum, a recent Cochrane review found no data to suggest that infant growth is affected when COCs are started early in lactation (Truitt et al. *Contraception*. 2003;68:233).
7. Risks vs. benefits: there is an overemphasis on the risks of COCs. Although there are many non-contraceptive benefits of COCs, only a few minor ones are mentioned. This leads to an unbalanced presentation of risks and benefits. Again, this appears due to selective use of older studies to suggest risks. For example, even recent case-control studies which include exposure to low-dose pills have consistently found a protective effect against ovarian cancer, yet this pivotal information is missing (Ness et al. *Epidemiology* 2001;12:307).

#### B. Patient label

1. Effectiveness: We suggest that the FDA reassess the use of the traditional table of contraceptive effectiveness for patients. Preliminary evidence indicates that many women cannot understand these numerical tables.(Steiner et al. *Obstet Gynecol* 2003;102:709) Based on this preliminary study, we suggest that the FDA recommend/require that COC manufacturers conduct label comprehension studies.

2. Missed pills—At another recent WHO meeting of contraceptive experts (Selected Practice recommendations for Contraceptive Use, April 2004), data relevant to missed pills were reviewed. According to the evidence, missing up to 2 pills, even at the beginning or end of a cycle, should not significantly increase the risk of pregnancy. Furthermore, a new FHI study showed that women did not understand the previous complicated WHO missed pill instructions. Based on the evidence, recommendations regarding missed pills were updated and vastly simplified. These new recommendations will soon be posted on the WHO website.

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