

Ibis
Reproductive
Health

May 3, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket number 2000D-1350 in the *Federal Register* 5 March 2004 (Volume 69)

Dear Sir/Madam:

We are pleased to submit comments on the draft Guidance for Industry: Labeling for Combined Oral Contraceptives dated March 2004. We write on behalf of Ibis Reproductive Health, a non-profit organization in Cambridge, MA, that conducts clinical and social science research, analyzes policy and advocates for medical reform, all as ways to improve reproductive health and autonomy.

We are concerned with a number of changes in the 2004 Guidance for Industry as compared to the 2000 version, and would like to call your attention to the following points:

1. Effectiveness table In the provider labeling, the table of contraceptive effectiveness in the 2000 Guidance, based on Trussell *et al.*¹ has been replaced by a simplified table in the 2004 Guidance. We argue that this new table is far less useful than the previous version because:

- It makes no distinction between perfect and typical effectiveness rates. The numbers seem to reflect typical rates for some methods such as spermicides and condoms, yet for other methods such as POPs, we cannot determine whether the figure provides the perfect or typical use rate, and in fact are unclear on where this information comes from.
- It omits estimates for periodic abstinence, cap, sponge, withdrawal, and female condom, and makes no distinction between male and female sterilization. It further omits the "chance" category, which provides a useful baseline.
- Its five grouped categories of methods implies that all methods within each category have similar effectiveness, whereas in fact effectiveness can vary greatly with a category.
- It includes no citations, referring only to FDA trials and "medical literature."
- It includes no caveat, as the Trussell table does, that effectiveness can vary with certain characteristics of the user.

We believe that the Trussell table in the 2000 Guidance represents the most comprehensive and careful summary of the literature on contraceptive effectiveness. However, it has come under criticism for providing point estimates for methods that actually have large user-dependent variability in

¹ Trussell J. Contraceptive efficacy. In: Hatcher RA, Trussell J, Stewart F, Cates W, Stewart G, Guest F, Kowal D, eds. *Contraceptive Technology*, 17th revised edition. Ardent Media: New York, NY; 1998. p. 779-844.

effectiveness. To address this, we suggest that instead of making the numbers more approximate, more detail should be included, such as ranges of effectiveness or lists of strong predictors of effectiveness for each method. If this is perceived as too much information, simple changes to the presentation of the data can make it more intuitively interpretable, such as using bar graphs or dot-and-whisker plots.

We apply these comments only to the table in the health care provider label, not the consumer label. Providers are trained to interpret complex method information, and when the table was simplified for the 2004 Guidance, it substantially reduced providers' ability to consider COCs in the context of other contraceptive methods, of a particular patient, or of the relevant literature.

2. COCs as emergency contraception The FDA has acknowledged that eighteen brands of COCs can be used safely and effectively as emergency contraception (EC) after unprotected intercourse.² The 2000 Guidance included information in the labeling for healthcare providers on the use of COCs as EC; however, with the change in the effectiveness table on line 90 of the 2004 Guidance, this information has been removed. We would like to see this information reinstated in some form and believe it should also be included in the patient labeling. Incorporating this information in the labels of relevant formulations of COCs would increase provider and patient awareness of the use of COCs as EC and could prevent pregnancies after unprotected intercourse.

3. Annual exams We are disappointed with the addition of the statement "Women who are using oral contraceptives should have an annual history and physical examination..." on line 290. The bundling of these services with COC provision and the frequency of the health maintenance visit are troubling. Most professional organizations no longer require clinical breast and pelvic exams in order to provide COCs, and as Stewart *et al.* point out, requiring such visits likely limits access to contraceptives for some women.³ The only portion of the physical examination that is relevant to COC use is blood pressure measurement, as hypertension is a contraindication to COC use and some women develop this condition while on COCs. Even if the labeling were to recommend a periodic health maintenance exam, the frequency of this visit should be consistent with the medical evidence and the recommendations of leading professional organizations. Women who are at low risk and have had three prior negative screening tests for cervical dysplasia are candidates for screening every two to three years.⁴ In addition, little evidence supports the utility of clinical breast exams to detect early breast cancer, especially in women under the age of 40.⁵

The language in the 2000 Guidance for Industry was more consistent with the evidence related to supervising COC use. Under "Physical examination and follow-up" on page 8, blood pressure measurement is the only component of the physical exam recommended to be performed with some frequency. We suggest that lines 288-292 in the current Guidance be replaced with this paragraph from page 8 of the 2000 Guidance.

4. Non-contraceptive health benefits A section on "Non-contraceptive Health Benefits" of COCs appears both in the current labeling and in the 2000 Guidance (pages 11-12). This information appears

² Food and Drug Administration. Prescription drug products: certain combined oral contraceptives for use as postcoital emergency contraception. Federal Register 1997; 62:8610-2.

³ Stewart FH, Harper CC, Ellertson CE, Grimes DA, Sawaya GF, Trussell J. Clinical breast and pelvic examination requirements for hormonal contraception: Current practice vs. evidence. JAMA 2001 May 2;285(17):2232-9.

⁴ American College of Obstetricians and Gynecologists Committee on Practice Bulletins-Gynecology. Cervical cytology screening. ACOG Practice Bulletin, No. 45, August 2003.

⁵ U.S. Preventive Services Task Force. Breast Cancer Screening, February 2002. Available from <http://www.ahrq.gov/clinic/uspstf/uspstfbrca.htm>. Accessed 26 March 2004.

to have been removed from the sections titled “Possible Health Benefits” on page 11 and 19 of the 2004 Guidance. Abundant data have established that COC use decreases the risk of ovarian and endometrial cancer, of benign breast disease, and of symptomatic pelvic inflammatory disease.⁶ OC use also prevents ectopic pregnancy and improves hirsutism and acne.⁶ A minority of U.S. women are familiar with these important non-contraceptive benefits,⁷ and information in the labeling of the medication offers an additional opportunity to educate both physicians and consumers about the advantages of using COCs. We recommend adding this section from the 2000 Guidance back into the current document.

5. Nursing mothers We welcomed the changes related to COC use during lactation that appeared in the 2000 Guidance, which were a clear improvement over the current COC labeling. On page 10 of the 2000 Guidance under the heading “Nursing mothers,” the wording acknowledged the possibility of an effect of COCs on the quantity and quality of breast milk. However, by omitting the recommendation that COCs be avoided during lactation, the Guidance recognized the poor quality of the data upon which this recommendation had been based, a fact that a recent review of the topic highlighted.⁸ The 2000 Guidance even had an additional section in the patient labeling that specifically explained COC use during breastfeeding. The American College of Obstetricians and Gynecologists has issued a statement saying that COCs can be appropriate for well-nourished breastfeeding women after milk flow is well established.⁹ We recommend that lines 388-391 of the 2004 Guidance be replaced with the language regarding COC use during lactation from the 2000 Guidance.

6. Start date We were surprised that the current Guidance requires that the instructions for starting a particular brand of COC be consistent with the clinical trials for that brand (lines 521-523). This differs from the 2000 Guidance (pages 14-15), which described all three common starting schedules (first day of menses, Sunday, or any day if pregnancy is reasonably unlikely). The 2000 Guidance was consistent with the practice patterns of several leading authorities that recommend any one of the three starting schedules.^{6,10} Two trials have examined starting COCs at the time of clinician visit, regardless of where a woman is in her cycle, a practice called Quick Start.^{11,12} These trials demonstrated that Quick Start COC initiation does not worsen side-effects and may improve continuation. Furthermore, the current Guidance gives no information about how to start COCs after a miscarriage, abortion or delivery. Nor does it specify how to start COCs if a user wants to change brands or switch contraceptive methods. We recommend that the information regarding starting COCs provided in the 2000 Guidance (pages 14-16) be reincorporated into the current draft.

⁶ Hatcher RA, Guillebaud. The pill: combined oral contraceptives. In: Hatcher RA, Trussell J, Stewart F, Cates W, Stewart G, Guest F, Kowal D, eds. *Contraceptive Technology*, 17th revised edition. Ardent Media: New York, NY; 1998. p. 405-66.

⁷ Picardo CM, Nichols M, Edelman A, Jensen JT. Women's knowledge and sources of information on the risks and benefits of oral contraception. *J Am Med Womens Assoc.* 2003 Spring;58(2):112-6.

⁸ Truitt ST, Fraser AB, Grimes DA, Gallo MF, Schulz KF. Combined hormonal versus nonhormonal versus progestin-only contraception in lactation (Cochrane Review). In: *The Cochrane Library*, Issue 3, 2003. Oxford: Update Software.

⁹ ACOG Committee on Practice Bulletins-Gynecology. The use of hormonal contraception in women with coexisting medical conditions. *ACOG Practice Bulletin*. Number 18, July 2000.

¹⁰ World Health Organization. Selected practice recommendations for contraceptive use. Available from: http://www.who.int/reproductive-health/publications/rhr_02_7/rhr_02_07_questions.html. Accessed 5 February 2004.

¹¹ Lara-Torre E, Schroeder B. Adolescent compliance and side effects with Quick Start initiation of oral contraceptive pills. *Contraception.* 2002;66:81-85.

¹² Westhoff C, Kerns J, Morrioni C, Cushman LF, Tiezzi L, Murphy PA. Quick start: novel oral contraceptive initiation method. *Contraception.* 2002;66:141-145.

7. **Contraindications** The wording of several of the contraindications appears to have changed since the 2000 Guidance.

- “Liver tumors, now or in the past, or liver disease” (line 108) implies that any history of liver disease, rather than acute or active liver disease, is a contraindication to COC use. The section on liver disease from the 2000 Guidance (page 8) was much more accurate and we recommend a return to the wording contained therein.
- Additionally, “undiagnosed abnormal genital bleeding” was removed from the list of contraindications in the 2000 Guidance, and instead was explained under the heading of “Warnings” (page 7). We recommend a return to the wording present in the 2000 Guidance.
- The addition of the contraindication listed as “any condition predisposing to thrombotic diseases” (line 109) is unacceptably vague. This contraindication, along with “congenital hypercoagulopathies” (line 115), seems to refer to the increased risk of thrombosis associated with various genetic mutations, such as factor V Leiden. However, if there is a consensus to include these as contraindications, the Guidance should state clearly which defects are strict contraindications and which are relative contraindications. For example, women homozygous for factor V Leiden absolutely should not be prescribed COCs, while heterozygosity for this mutation is a relative contraindication.¹³ Furthermore, the addition of these contraindications implies that a physician might be liable for malpractice if he or she prescribed COCs to a woman who was later discovered to have one of these mutations (or some other thrombophilic condition). Current recommendations advise against routine screening for thrombophilic markers,⁹ and the addition of these vague contraindications appears to have been added to protect the pharmaceutical industry rather than to educate physicians and consumers. We recommend deleting these contraindications and maintaining the warning about coagulation disorders on lines 169-170. Our concerns also apply to the text in the patient labeling (lines 571-588).
- The 2000 Guidance accurately listed the true thrombotic contraindications to COC use: deep vein thrombosis (current or history), pulmonary embolism (current or history), ischemic heart disease (current or history), and history of cerebrovascular accidents (page 4). The current Guidance has added back “thrombophlebitis” (line 111) as a contraindication, despite the lack of data suggesting an increased risk of serious thromboembolism associated with COC use after prior superficial thrombophlebitis. The WHO Medical Eligibility Criteria list only deep venous thrombosis or pulmonary embolus as true contraindications,¹⁴ and COC labeling should be consistent with existing evidence. Our concerns also apply to the text in the patient labeling (lines 571-588).
- Finally, we are concerned about the warning on line 582 regarding migraine headaches. The term “severe migraine headaches” may be misunderstood by some women. The association

¹³ Girolami A, Spiezia L, Girolami B, Vianello F. Tentative guidelines and practical suggestions to avoid venous thromboembolism during oral contraceptive therapy. *Clin Appl Thromb Hemost* 2002 Apr;8(2):97-102.

¹⁴ World Health Organization. Improving access to quality care in family planning: Medical eligibility criteria for contraceptive Use, 2nd ed. Ref. WHO/RHR/00.02. Available from: http://www.who.int/reproductivehealth/publications/RHR_00_2_medical_eligibility_criteria_second_edition/rhr_00_02_cocs.html. Accessed 17 December 2003.

between COC use and stroke has recently been called into question,¹⁵ and if there truly is a link between the two, only women with migraine with aura are at increased risk.¹⁶ Line 582 should specifically list “aura” or “neurologic symptoms” along with migraine as a contraindication.

Thank you for the opportunity to comment.

Sincerely,



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Acting President



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¹⁵ Chan W-S, Ray J, Wai EK, Ginsburg S, Hannah ME, Corey PN, Ginsberg JS. Risk of stroke in women exposed to low-dose oral contraceptives: a critical evaluation of the evidence. Arch Intern Med 2004 Apr; 164:741-7.

¹⁶ Bousser MG, Conard J, Kittner S, de Lignieres B, MacGregor EA, Massiou H, Silberstein SD, Tzourio C. Recommendations on the risk of ischaemic stroke associated with use of combined oral contraceptives and hormone replacement therapy in women with migraine. The International Headache Society Task Force on Combined Oral Contraceptives & Hormone Replacement Therapy. Cephalalgia 2000 Apr;20(3):155-6.