

ATTACHMENT 1

**Wyeth-Ayerst Comments to 2000 Draft Labeling Guidance for
Combined Oral Contraceptives**

Wyeth-Ayerst Comments to June 2000 Draft Guidance Entitled "Combined Oral Contraceptives – Labeling for Health Care Providers and Patients"

II. LABELING FOR HEALTHCARE PROVIDERS

Draft Guidance Text, Boxed Warning, Lines 159 – 164:

WARNING-CIGARETTE SMOKING

Cigarette smoking increases the risk of serious cardiovascular side effects from COC use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use COCs should be strongly advised not to smoke.

PROPRIETARY NAME (*Established Name*)

Supplied by manufacturer

Wyeth-Ayerst comments: The Boxed Warning is important information at the beginning of the label. We believe, however, that the placement of the Boxed Warning would be more appropriate after the product name. This placement is in keeping with the majority of products that contain a Boxed Warning and health care providers are accustomed to this placement. In addition, the Boxed Warning placed directly under the product name clearly associates the warning with the product. Wyeth-Ayerst therefore proposes to move the Boxed Warning below the Proprietary name.

Proposed Labeling:

PROPRIETARY NAME (*Established Name*)

Supplied by manufacturer

WARNING-CIGARETTE SMOKING

Cigarette smoking increases the risk of serious cardiovascular side effects from COC use. The risk increases with age and with heavy smoking (15 or more cigarettes per day) and is quite marked in women over 35 years of age. Women who use COCs should be strongly advised not to smoke.

Addition of A New Subsection To The Draft Guidance

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes that a new subsection entitled "Clinical Studies" be added to the **CLINICAL PHARMACOLOGY** section of the draft guidance.

This subsection would identify endpoints and describe efficacy, study design, population and findings that support the indication, e.g., prevention of pregnancy, treatment of acne. Furthermore, this additional subsection would conform COC labeling to other product labeling.

Proposed Labeling:

Clinical Studies

This section will be specific for the product in question and should include information concerning the appropriate endpoints to assess the efficacy for the indication sought.

A concise and objective description of the pivotal efficacy studies should include brief summaries of the following:

a. study design;

b. demographics of the intent-to-treat study population;

c. study results;

Draft Guidance Text, CLINICAL PHARMACOLOGY, Lines 182-187:

Mode of Action

The primary mechanism by which combined estrogen-progestin oral contraceptives prevent conception is suppression of ovulation. Other possible mechanisms include changes in the cervical mucus that inhibit sperm penetration and alterations of the endometrium that reduce the likelihood of implantation.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the removal of "possible" when discussing other actions for preventing conception. In addition to the suppression of ovulation, COCs provide contraceptive effects by thickening cervical mucus and suppressing the development of the endometrium. These mechanisms are supported by published literature.

Proposed Labeling:

The primary mechanism by which combined estrogen-progestin oral contraceptives prevent conception is suppression of ovulation. Secondary actions include changes in the cervical mucus that inhibit sperm penetration and alterations of the endometrium that reduce the likelihood of implantation.

References:

Appendix 1 contains copies of the following references to support our comments and proposed labeling.

- Rossmannith WG, Steffens D and Schramm G: A comparative randomized trial on the impact of two low-dose oral contraceptives on ovarian activity, cervical permeability, and endometrial receptivity. *Contraception* 56(1): 23-30, 1997.
- Gaspard UJ, Dubois M, Gillain D, et al: Ovarian function is effectively inhibited by a low-dose triphasic oral contraceptive containing ethinyl estradiol and levonorgestrel. *Contraception* 29(4): 305-318, 1984.
- Somkuti AS, Sun J, Yowell CW, et al: The effect of oral contraceptive pills on markers of endometrial receptivity. *Fertil Steril* 65(3): 484-488, 1996.
- Chretien FC, Sureau C and Neau C: Experimental study of cervical blockage induced by continuous low-dose oral progestogens. *Contraception* 22(5): 445-456, 1980.
- Spona J et al: Mode of action of triphasic oral contraception. (in) The Development of a New Triphasic Oral Contraceptive; RB Greenblatt, ed.; (MTP Press Limited, International Medical Publishers, 1980), pp. 51-68.

Draft Guidance Text, INDICATIONS AND USAGE, Lines 207-213:

Efficacy

If COCs are used as recommended in their approved labeling, the chance of becoming pregnant during the first year of use is 0.1 percent. However, typical pregnancy rates are estimated to be 5 percent (Table 1 - Trussell et al. 1998). Rates of effectiveness vary by factors that affect ability to conceive (including age), frequency of sexual intercourse, and how correctly and consistently the method is used.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes that FDA consider retaining the sentence, "Oral contraceptives are highly effective." as stated in the 1994 COC Labeling Guidance. This statement is supported by the data in Table 1 – Trussell, et al, 1998 cited in the Draft Guidance.

Proposed Labeling:

Efficacy

Oral contraceptives are highly effective. If COCs are used as recommended in their approved labeling, the chance of becoming pregnant during the first year of use is 0.1 percent. However, typical pregnancy rates are estimated to be 5 percent (Table 1 - Trussell et al. 1998). Rates of effectiveness vary by factors that affect ability to conceive (including age), frequency of sexual intercourse, and how correctly and consistently the method is used.

Draft Guidance Text, TABLE 1, Lines 227-323:

Wyeth-Ayerst Comments: Within Table 1, Wyeth-Ayerst requests that the branded names "Norplant" and "Norplant 2" be replaced with the generic name "Levonorgestrel implants". The "Norplant[®] System" is the proprietary name of the Wyeth-Ayerst six capsule levonorgestrel implant product. A proprietary name for the Wyeth-Ayerst two rod levonorgestrel implant product has not yet been chosen.

Proposed Labeling:

~~Norplant and Norplant 2~~ Levonorgestrel implants

Draft Guidance Text, TABLE 1, Lines 274-278, 284-285:

- 9 The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Nordette or Levlén (1 dose is 2 light orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlén (1 dose is 4 yellow pills) (62 FR 8612; February 25, 1997).*

*Alesse was approved as safe and effective for emergency contraception subsequent to the February 1997 *Federal Register* notice.

Wyeth-Ayerst Comments: Wyeth-Ayerst requests the removal of the footnote to Emergency Contraception from the Trussell Table specifically with regard to the mention of its oral contraceptive products. Wyeth-Ayerst does not market these products for such use. Products which are approved and marketed for emergency contraception include PREVENT[™] Emergency Contraceptive Kit and Plan B[™].

Proposed Labeling:

9 The treatment schedule is one dose within 72 hours after unprotected intercourse, and a second dose 12 hours after the first dose. The Food and Drug Administration has declared the following brands of oral contraceptives to be safe and effective for emergency contraception: Ovral (1 dose is 2 white pills), Alesse (1 dose is 5 pink pills), Norello or Levlen (1 dose is 2 light orange pills), Lo/Ovral (1 dose is 4 white pills), Triphasil or Tri-Levlen (1 dose is 4 yellow pills) (62 FR 8612, February 25, 1997).*

*Alesse was approved as safe and effective for emergency contraception subsequent to the February 1997 Federal Register notice.

Draft Guidance Text, TABLE 1, Lines 252-254:

Source: Trussell, J., "A Contraceptive Efficacy," in R.A. Hatcher, J. Trussell, F. Stewart, W. Cates, G.K. Stewart, F. Guest, D. Kowal, 1998, *Contraceptive Technology: Seventeenth Revised Edition*, Irvington Publishers.

Wyeth-Ayerst Comments: Wyeth proposes the addition of the words "Adapted from" when referring to the description of the source for the Trussell Table as it is not exactly the same as in the publication referenced above.

Proposed Labeling:

Source: Adapted from Trussell, J., "A Contraceptive Efficacy," in R.A. Hatcher, J. Trussell, F. Stewart, W. Cates, G.K. Stewart, F. Guest, D. Kowal, 1998, *Contraceptive Technology: Seventeenth Revised Edition*, Irvington Publishers.

Draft Labeling Guidance, CONTRAINDICATIONS, Line 291:

Pulmonary embolism (current or history)

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes that "thrombosis and thromboembolism" is more appropriate terminology for this contraindication which includes pulmonary embolism (current or history) as well as other thromboembolic events. Patients with thromboembolic disorders and a patent foramen ovale or atrial septal defect may not only experience pulmonary embolism, but emboli to the brain or extremities. Therefore, patients experiencing any thromboembolism should not take oral contraceptives due to the increased risk for thrombosis.

Proposed Labeling:

Pulmonary Thrombosis and thromboembolism (current or history)

References:

Appendix 2 contains copies of the following reference to support our comments and proposed labeling.

Harrison's Principle's of Internal Medicine. Fourteenth edition: p. 1303, 1998.

Draft Guidance Text, CONTRAINDICATIONS, and Lines 292 and 293:

Ischemic heart disease (current or history)

History of cerebrovascular accidents

Wyeth-Ayerst Comments: Wyeth Ayerst proposes that the contraindication "Ischemic heart disease (current or history)" be replaced with "Coronary artery disease" and that the contraindication "History of cerebrovascular accidents" be replaced with "Cerebrovascular

disease". The 1994 COC Labeling Guidance describes cerebrovascular and coronary artery disease as contraindications to COC use. A large number of international agencies and organizations active in the area of family planning policies and programs in collaboration with the World Health Organization (WHO) program area of Family Reproductive Health have established medical eligibility criteria for initiating and continuing COC use. WHO states that with regard to current ischemic heart disease, COCs should not be used. Among women with underlying vascular disease or with a demonstrated predisposition to thrombosis, the increased risk of thrombosis with COCs should be avoided.

Wyeth-Ayerst is in agreement with the 1994 COC Labeling Guidance, as well as the WHO recommendations, and requests that the FDA give due consideration to this position. Furthermore, the American College of Obstetricians and Gynecologists recently reiterated in their July 2000 Practice Bulletin entitled "The Use of Hormonal Contraception in Women with Coexisting Medical Conditions" that COCs are contraindicated in women with cerebrovascular disease.

Proposed Labeling:

~~Ischemic Heart Disease (current or history)~~ Coronary artery disease
~~History of Cerebrovascular~~ disease accidents

References:

Appendix 3 contains copies of the following references to support our comments and proposed labeling.

- WHO: Improving Access to Quality Care in Family Planning (1996), p.18.
ACOG Practice Bulletin Number 18: The use of hormonal contraception in women with coexisting medical conditions. July 2000.
WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception: Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. *Lancet* 349: 1202-1209, 1997.
Lewis, MA et al: The use of oral contraceptives and the occurrence of acute myocardial infarction in young women: Results from the transnational study on oral contraceptives and the health of young women. *Contraception* 56: 129-140, 1997
Stampfer, MEJ et al: A prospective study of past use of oral contraceptive agents and risk of cardiovascular diseases. *N Engl J Med* 319(20): 1313-1317, 1988.
Rosenberg, L et al: Oral contraceptive use in relation to nonfatal myocardial infarction. *Am J Epidemiol* 111(1): 59-66, 1980.
WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception: Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 348(9026): 498-505, 1996.
Hannaford, PC et al: Oral contraception and stroke. Evidence from the Royal College of General Practitioners' Oral Contraception Study. *Stroke* 25(5): 935-942, 1994.
Heinemann, LAJ et al: Case-control study of oral contraceptives and risk of thromboembolic stroke: Results from international study on oral contraceptives and health of young women. *Br Med J* 315: 1502-1504, 1997.
WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception: Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: Results of an international, multicentre, case-control study. *Lancet* 348(9026): 505-510, 1996.
Royal College of General Practitioners: Incidence of arterial disease among oral contraceptive users. Royal College of General Practitioners' oral contraception study. *J Royal Coll Gen Pract* 33(247): 75-82, 1983.

Draft Guidance Text, CONTRAINDICATIONS, Line 294:

Valvular heart disease with complications

Wyeth-Ayerst Comments: Wyeth-Ayerst agrees with FDA's proposal for inclusion of a contraindication for patients with valvular heart disease who may be predisposed to thrombus formation. In the Draft Guidance, this is a concept conveyed through the contraindication "Valvular heart disease with complications." However, Wyeth-Ayerst believes that the term "thrombogenic valvulopathies and thrombogenic rhythm disorders" more accurately describes the complication which is of concern to patients taking combination oral contraceptives, specifically valvulopathies and rhythm disorders that cause an increased risk for thrombus formation. This change is consistent with the complications described in the **Valvular heart disease** section in **WARNINGS**. Pulmonary hypertension, atrial fibrillation and subacute bacterial endocarditis are all factors which increase the risk of thrombosis in patients with valvular heart disease.

Proposed Labeling:

~~Valvular heart disease with complications~~ Thrombogenic valvulopathies and thrombogenic rhythm disorders

Draft Guidance Text, CONTRAINDICATIONS, Line 295:

Severe hypertension

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes to change the contraindication "Severe hypertension" to "Uncontrolled hypertension". The term "severe" is a general term that may hold various meanings to different health care providers. Without providing a definition of "severe," a health care provider will arbitrarily assign his/her own definition. This may result in depriving some women with hypertension of effective contraception with COCs. The risks and complications of maternal and fetal morbidity associated with hypertension during pregnancy may be greater than the risks of blood pressure elevations occurring with COC use. Furthermore, the increases in systolic and diastolic blood pressure with COC use have been reported to be small and usually within the normal range. These small increases may not be clinically relevant in a patient whose blood pressure is, or can be, controlled with antihypertensive medication.

The term "uncontrolled hypertension" defines the population of women who may be placed at additional risks with further increases in blood pressure because these women are not being treated or cannot be adequately controlled with current therapies. The July 2000 ACOG Practice Bulletin entitled "The Use of Hormonal Contraception in Women with Coexisting Medical Conditions" states that, "Women with well-controlled and monitored hypertension who are aged 35 years or younger are appropriate candidates for a trial of combination OCs formulated with 35 mcg or less of estrogen, provided they are otherwise healthy, show no evidence of end-organ vascular disease, and do not smoke cigarettes. If blood pressure remains well controlled with careful monitoring several months after initiating OCs, use can be continued."

Proposed Labeling:

~~Severe~~ Uncontrolled hypertension

References:

Appendix 4 contains copies of the following references to support our comments and proposed labeling.

- JNC VI, The sixth report of the Joint National Committee on the detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 157: 1997.
- ACOG. The use of hormonal contraception in women with coexisting medical conditions. *ACOG Practice Bulletin*. 18: 2000.
- Knijff SCM, Goorissen EM, et al, editors. Summary of Contraindications to Oral Contraceptives. New York: Parthenon Publishing Group; 2000, 219-230.

Draft Guidance Text, CONTRAINDICATIONS, Line 298:
Major surgery with prolonged immobilization

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes that "Major surgery with prolonged immobilization" be deleted from the **CONTRAINDICATIONS** section. The 1994 COC Labeling Guidance describes that a 2- to 4- fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism and during and following prolonged immobilization. Furthermore, the American College of Obstetricians and Gynecologists recently stated in their July 2000 Practice Bulletin entitled "The Use of Hormonal Contraception in Women with Coexisting Medical Conditions" that risks associated with stopping OCs one month or more before major surgery and during periods of prolonged immobilization should be balanced against the risks of an unintended pregnancy.

Wyeth-Ayerst requests that the FDA consider placement of this concept in **WARNINGS** (see Page 13 of this document: **WARNINGS** Line 349-351). The proposed statement to be added to **WARNINGS** is as follows: "If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk and thromboembolism and during prolonged immobilization."

Proposed Labeling:

Major surgery with prolonged immobilization

References:

Appendix 5 contains copies of the following references to support our comments and proposed labeling.

- ACOG Practice Bulletin Number 18: The use of hormonal contraception in women with coexisting medical conditions. July, 2000.
- Guillebaud, J: Surgery and the pill. *Br Med J* 291: 498-499, 1985.
- Robinson, GE et al: Changes in haemostasis after stopping the combined contraceptive pill: Implications for major surgery. *Br Med J* 302: 269-271, 1991.
- The Gynecological Endocrinology and Reproductive Medicine Study Group: Is it advisable to discontinue oral hormonal contraceptives before elective surgery? *Der Frauenarzt* 37(7): 730-734, 1993.

Draft Guidance Text, CONTRAINDICATIONS, Line 310:

Known or suspected carcinoma of the breast or personal history of breast cancer

Wyeth-Ayerst Comments: Wyeth-Ayerst believes that the phrase “known or suspected carcinoma of the breast” adequately encompasses the phrase “personal history of breast cancer”. Wyeth-Ayerst, therefore, proposes the deletion of the phrase “or personal history of breast cancer”.

The 1994 COC Labeling Guidance also describes “other known or suspected estrogen-dependent neoplasia” as a contraindication to COC use. Wyeth-Ayerst proposes that the FDA reconsider retaining the phrase “or other estrogen dependent neoplasia” based upon the support of the published literature as provided with this submission. The risk for progression of these conditions may be increased among women with current or history of known or suspected estrogen-dependent neoplasia.

Proposed Labeling:

Known or suspected carcinoma of the breast ~~or personal history of breast cancer~~ or other estrogen-dependent neoplasia

References:

Appendix 6 contains copies of the following references to support our comments and proposed labeling.

- ACOG Practice Bulletin Number 18: The use of hormonal contraception in women with coexisting medical conditions. July 2000.
- Milewich, L: Steroid hormone receptors in gynecologic and mammary neoplasms. *Gynecologic Oncology* Vol 4; Chap 33 1-19.
- Gao, YL et al: Cytoplasmic estrogen and progesterone receptors in primary cervical carcinoma: clinical and histopathologic correlates. *Am J Obstet and Gynecol* 146: 299-306, 1983.
- Holt, JA et al: Estrogen and progestin binding in cytosols of ovarian adenocarcinomas. *Obstetrics and Gynecology* 53(1): 50-58, 1979.
- King, RJB: Biology of female sex hormone action in relation to contraceptive agents and neoplasia. *Contraception* 43(6): 527-542, 1991.

Draft Guidance Text, CONTRAINDICATIONS, Line 311:

Liver tumors (benign and malignant), active liver disease

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes that the FDA’s Draft Guidance contraindication be revised as follows: “Liver tumors (benign and malignant), liver disease as long as liver function tests have not returned to normal.” In support of this proposed labeling, Speroff et al, the editors of Clinical Gynecologic Endocrinology and Infertility (Sixth Edition), have stated, with regard to hepatic disease, that oral contraception can be utilized when liver function tests return to normal.

Proposed Labeling:

Liver tumors (benign and malignant), active liver disease as long as liver function tests have not returned to normal

References:

Appendix 7 contains copies of the following references to support our comments and proposed labeling.

- Speroff, L et al: *Clinical Gynecologic Endocrinology and Infertility*, Sixth Edition; C Mitchell, ed., (Baltimore, MD: Lippincott Williams & Wilkins, 1999), p. 920.
- Lindberg, MC: Hepatobiliary complications of oral contraceptives. *Journal of General Internal Medicine* 7: 199-209, 1992.
- Cohen, L et al: Pregnancy, oral contraceptives, and chronic familial jaundice with predominantly conjugated hyperbilirubinemia. *Gastroenterology* 62(6): 1182-1190, 1972.
- Kaplowitz, N et al: Drug-induced hepatotoxicity. *Annals of Internal Medicine* 104: 826-839, 1986.
- Orme, MLE et al: Clinical pharmacokinetics of oral contraceptive steroids. *Clinical Pharmacokinetics* 8: 95-136, 1983.
- Aldercreutz, H: Oestrogen metabolism in liver disease. *J Endocr* 46: 129-163, 1970.

Draft Guidance Text, CONTRAINDICATIONS, Line 313:

Heavy smoking (≥ 15 cigarettes per day) and over age 35

Wyeth-Ayerst Comments: Wyeth-Ayerst believes that COC labeling regarding smoking and COC use should take into consideration the needs of individual patients. Wyeth-Ayerst is in agreement with the 1994 COC Labeling Guidance regarding cigarette smoking as discussed in the **BOXED WARNING** and under **WARNINGS**. The concepts in the 1994 COC Labeling Guidance give health care providers the essential information needed to adequately weigh the risks of pregnancy against those risks associated with COC use in their patients who smoke. It further assists health care providers when making a clinical judgement regarding the selection of a birth control method for these patients.

For these reasons, Wyeth-Ayerst requests that FDA consider retaining the concepts addressed in the 1994 COC Labeling Guidance by retaining the **BOXED WARNING**, deleting the statement regarding smoking in **CONTRAINDICATIONS**, and adding a sentence to the **WARNINGS** section regarding smoking. (See Page 10 of this document, **WARNINGS**, Lines 320-325.)

Proposed Labeling:

~~Heavy smoking (≥ 15 cigarettes per day) and over age 35~~

References:

Appendix 8 contains copies of the following references to support our comments and proposed labeling.

- ACOG Practice Bulletin Number 18: The use of hormonal contraception in women with coexisting medical conditions. July 2000.
- WHO Technical Report Series 877: Cardiovascular disease and steroid hormone contraception, Geneva 1998.
- WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception: Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. *Lancet* 349: 1202-1209, 1997.
- Lewis, MA et al: The use of oral contraceptives and the occurrence of acute myocardial infarction in young women: Results from the transnational study on oral contraceptive and the health of young women. *Contraception* 56: 129-140, 1997.
- Rosenberg, L et al: Myocardial infarction and cigarette smoking in women younger than 50 years of age. *JAMA* 253(20): 2965-2969, 1985.

- Croft, P and Hannaford, PC: Risk factors for acute myocardial infarction in women: Evidence from the Royal College of General Practitioners' oral contraception study. *BMJ* 298: 165-168, 1989.
- Layde, PM and Beral, V: Further analysis of mortality in oral contraceptive users: Royal College of General Practitioners' Oral Contraception Study. *Lancet* 1: 541-546, 1981.
- Goldbaum, GM et al: The relative impact of smoking and oral contraceptive use on women in the United States. *JAMA* 258(10): 1339-1342, 1987.
- Royal College of General Practitioners: Incidence of arterial diseases among oral contraceptive users. Royal College of General Practitioners' oral contraception study. *J Royal Coll Gen Pract* 22(247): 75-82, 1983.
- Stadel BV: Oral contraceptives and cardiovascular disease. *NEJM* 305(12, Part 2): 672-677, 1981.
- Shapiro, S et al: Oral-contraceptive use in relation to myocardial infarction. *Lancet* 1(8119): 743-747, 1979.
- WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception: Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. *Lancet* 348(9026): 498-505, 1996.
- WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception: Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: Results of an international, multicentre, case-control study. *Lancet* 348(9026): 505-510, 1996.
- Petitti, DB et al: Stroke in users of low-dose oral contraceptives. *NEJM* 335(1): 8-15, 1996.
- Petitti, DB and Wingerd, J: Use of oral contraceptives, cigarette smoking, and risk of subarachnoid haemorrhage. *Lancet* 2(8083): 234-236, 1978.
- Collaborative Group for the Study of Stroke in Young Women: Oral contraceptives.

Draft Guidance Text, WARNINGS, Lines 320-325:

1. Cardiovascular disease

COC use is associated with an increase in the incidence of cardiovascular disease, primarily because of an increased risk of thrombosis, rather than through an atherogenic mechanism. The degree of risk appears to be related primarily to the estrogen dosage. This increased risk is limited to the period of COC use and disappears on cessation of use.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the revision of text in the **Cardiovascular disease** section of **WARNINGS** describing that there are reports of arterial and venous thrombotic and thromboembolic events with COC use.

Wyeth-Ayerst also proposes to add the sentence "Cigarette smoking increases the risk of serious cardiovascular side effects from COC use." to **WARNINGS** in conjunction with our proposal to delete the Contraindication "Heavy smoking (≥ 15 cigarettes per day) and over age 35". The justification and references for this proposed change have been previously described in **CONTRAINDICATIONS** on Page 9 of this document.

Proposed Labeling:

1. Cardiovascular disease

COC use is associated with an increased risk of arterial and venous thrombotic and thromboembolic events in the incidence of cardiovascular disease, primarily because of an increased risk of thrombosis, rather than through an atherogenic mechanism. The degree of risk appears to be related primarily to the estrogen dosage. This increased risk is limited to the period of COC use and disappears on cessation of use. Cigarette smoking increases the risk of serious cardiovascular side effects from COC use.

Draft Guidance Text, WARNINGS, Lines 327-340:

a. Deep vein thrombosis, pulmonary embolism

Use of COCs is associated with a risk of venous thromboembolism which is 3 to 6 times higher than that among nonusers. Smoking does not appear to contribute to the risk of venous thromboembolic events.

Wyeth-Ayerst Comments: Wyeth-Ayerst agrees with FDA that COC use increases the risk of venous thromboembolic disease. However, we believe this risk is best described as an absolute risk (4 cases per 10,000 women) rather than a relative risk (3 to 6 times higher). The comparison of increased venous thromboembolism risk from COC use compared to non-users and to the increased risk from pregnancy allows the physician and patient to put this overall risk in perspective. Wyeth-Ayerst, therefore, proposes the revision of text regarding venous thromboembolism to discuss absolute risk.

Wyeth-Ayerst also proposes changing the title to "**Thrombosis and thromboembolism**" to encompass more thrombotic events than just deep vein thrombosis and pulmonary embolism. There have been reports of thrombi to other parts of the body.

Proposed Labeling:

~~a. Deep vein thrombosis, pulmonary embolism~~

a. Thrombosis and thromboembolism

~~Use of COCs is associated with a risk of venous thromboembolism which is 3 to 6 times higher than that among nonusers. Smoking does not appear to contribute to the risk of venous thromboembolic events.~~

Epidemiological studies have shown that the risk of venous thromboembolic (VTE) disorders is increased by the use of oral contraceptives. The approximate occurrence of VTE in users of oral contraceptive with low estrogen content (<50 ug ethinyl estradiol) is up to 4 cases per 10,000 women-years compared to 0.5-3 cases per 10,000 woman-years for non-users. Nevertheless, the risk is lower than that associated with pregnancy (i.e., 6 cases per 10,000 pregnancy-years).

References:

Appendix 9 contains copies of the following references to support our comments and proposed labeling.

- World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception: Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. *Lancet* 346: 1575-1582, 1995.
- Pini M, Scoditti U, Caliumi F, et al: Risk of venous thromboembolism and stroke associated with oral contraceptives. Role of congenital thrombophilias. *Recenti Progressi in Medicina* 87: 331-337, 1996.
- Koster T, Small RA, Rosendaal FR, et al: Oral contraceptives and venous thromboembolism: a quantitative discussion of the uncertainties. *J Int Med* 238: 31-37, 1995.
- Helmrich SP, Rosenberg L, Kaufman DW, et al: Venous thromboembolism in relation to oral contraceptive use. *Obstet Gynecol* 69(1): 91-95, 1987.
- Vessey M, Mant D, Smith A, et al: Oral contraceptives and venous thromboembolism: findings in a large prospective study. *Br Med J* 292: 526, 1986.
- Porter JB, Hunter JR, Jick H, et al: Oral contraceptives and nonfatal vascular disease. *J Am Coll Obstet Gynecol* 66(1): 1-4, 1985.
- Gerstman BB, Piper JM, Tomita DK, et al: Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. *Am J Epidemiol* 133(1): 32-37, 1991.
- Farmer RDT and Preston TD: The risk of venous thromboembolism associated with low oestrogen oral contraceptives. *J Obstet Gynaecol* 15: 195-200, 1995

Draft Guidance Text, WARNINGS, Lines 342-343:

The presence of factor V Leiden mutation and other hereditary coagulation disorders increases the risk of thromboembolic disease.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the addition of "or acquired" when discussing coagulation disorders. The addition of acquired thrombophilias is supported by several studies. It has been shown that antiphospholipid antibodies including the lupus anticoagulant and anticardiolipin antibodies are associated with both arterial and venous thrombosis. These antibodies can be associated with various autoimmune disorders including lupus, or with no known disease state. There are reports of oral contraceptive users with these antiphospholipid antibodies developing deep vein thrombosis or other venous thrombosis as well as arterial thrombosis such as myocardial infarction and cerebrovascular accidents. These antibodies may represent an increased risk for these complications in COC users.

Proposed Labeling:

The presence of factor V Leiden mutation and other hereditary or acquired coagulation disorders increases the risk of thromboembolic disease.

References:

Appendix 10 contains copies of the following references to support our comments and proposed labeling.

- Love, PE , Santoro, SA. Antiphospholipid antibodies: anticardiolipin and the lupus anticoagulant in systemic lupus erythematosus (SLE) and in non-SLE disorders. *Annals of Internal Medicine* 112:682-698, 1990.
- Wahl, DG et al. Risk for venous thrombosis related to antiphospholipid antibodies in systemic lupus erythematosus - a meta-analysis. *Lupus*:6:467-473, 1997.
- Bick, RL. Et al. Antiphospholipid-thrombosis syndromes. *Haemostasis*, 29:100-110, 1999.
- Asherton, RA. Complications of oral contraceptives and antiphospholipid antibodies: reply to the letter by Bruneau et al. *Arthritis and Rheumatism*, 31:575-576, 1988.

Draft Guidance Text, WARNINGS, Lines 345-347:

COC use is contraindicated for women who have active deep venous thrombosis or pulmonary embolism and for those who have a history of these conditions in association with estrogen use.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the deletion of this sentence from **WARNINGS** as this information is already stated in the **CONTRAINDICATIONS**. In addition, the contraindication for deep vein thrombosis includes patients without regard to presumed etiology.

Proposed Labeling:

~~COC use is contraindicated for women who have active deep venous thrombosis or pulmonary embolism and for those who have a history of these conditions in association with estrogen use.~~

Draft Guidance Text, WARNINGS, Lines 349-351:

Women who are immobilized for prolonged periods because of major surgery should not use COCs. For women undergoing surgery without prolonged immobilization, the advantages of COC use generally outweigh the risk.

Wyeth-Ayerst Comments: The 1994 COC Labeling Guidance describes that a 2- to 4- fold increase in relative risk of postoperative thromboembolic complications has been reported with the use of oral contraceptives. The relative risk of venous thrombosis in women who have predisposing conditions is twice that of women without such medical conditions. If feasible, oral contraceptives should be discontinued at least four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism during prolonged immobilization. Furthermore, the American College of Obstetricians and Gynecologists recently stated in their July 2000 Practice Bulletin entitled "The Use of Hormonal Contraception in Women with Coexisting Medical Conditions" that the risks associated with stopping OC's one month or more before surgery should be balanced against the risks of an unintended pregnancy. Wyeth-Ayerst, therefore, proposes that COC labeling reflect this information.

Proposed Labeling:

~~Women who are immobilized for prolonged periods because of major surgery should not use COCs.~~ If feasible, COCs should be discontinued for four weeks prior to and for two weeks after elective surgery of a type associated with an increase in risk of thromboembolism, and during prolonged immobilization. For women undergoing surgery without prolonged immobilization, the advantages of COC use generally outweigh the risk.

References:

Appendix 5 contains copies of the following references to support our comments and proposed labeling.

ACOG Practice Bulletin Number 18: The use of hormonal contraception in women with coexisting medical conditions. July, 2000.

Guillebaud, J: Surgery and the pill. *Br Med J* 291: 498-499, 1985.

Robinson, GE et al: Changes in haemostasis after stopping the combined contraceptive pill: Implications for major surgery. *Br Med J* 302: 269-271, 1991.

The Gynecological Endocrinology and Reproductive Medicine Study Group: Is it advisable to discontinue oral hormonal contraceptives before elective surgery? *Der Frauenarzt* 37(7): 730-734, 1993.

Draft Guidance Text, WARNINGS, Lines 353-354:

COC Use should preferably not begin until 2-3 weeks postpartum because of the risk of thrombosis.

Wyeth-Ayerst Comments: A large number of international agencies and organizations active in the area of family planning policies and programs in collaboration with the WHO program area of Family Reproductive Health have established medical eligibility criteria for initiating and continuing COC use relative to postpartum women. Wyeth-Ayerst is in agreement with the WHO recommendations which state that during the immediate postpartum period (<21 days), COC use is not recommended unless other more appropriate methods are not available or not acceptable. In addition, blood coagulation and fibrinolysis are essentially normalized by 3 weeks postpartum.

Proposed Labeling:

COC use should preferably not begin until 2–3 weeks postpartum, because of the risk of thrombosis.

References:

Appendix 11 contains copies of the following references to support our comments and proposed labeling.

WHO: Improving Access to Quality Care in Family Planning (1996), p 13.

Hannaford, PC and Webb, AMC (ed.): Evidence-Guided Prescribing of the Pill, (New York, USA: Parthenon Publishing Group, 1996), p. 232.

Guillebaud, J: Contraception after pregnancy. *Br J Fam Plann* 16(Suppl): 16-29, 1991.

Dahlman, T et al: Changes in blood coagulation and fibrinolysis in the normal puerperium. *Gynecol Obstet Invest* 20: 37-44, 1985.

Gray, RH et al: Postpartum return of ovarian activity in nonbreastfeeding women monitored by urinary assays. *J Clin Endocrin Metabol* 64(4): 645-650, 1987.

Hatherly, LI: Lactation and postpartum infertility: the use-effectiveness of natural family planning (NFP) after term pregnancy. *Clin Reprod Fertil* 3(4): 319-334, 1985.

Draft Guidance Text, WARNINGS, Lines 358-364:

b. Cerebrovascular disease

In women who do not smoke and do not have hypertension, the risk of ischemic stroke in users of COCs is increased by about 1.5 times compared with nonusers. The likelihood of hemorrhagic stroke is not increased among users of low-dose combined COCs who are under 35 years old and do not smoke or have hypertension. Women who have a history of stroke should not use COCs.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the deletion of the sentence “Women who have a history of stroke should not use COCs” under this subsection of **WARNINGS** as it is better stated as an absolute contraindication.

Proposed Labeling:

b. Cerebrovascular disease

In women who do not smoke and do not have hypertension, the risk of ischemic stroke in users of COCs is increased by about 1.5 times compared with nonusers. The likelihood of hemorrhagic stroke is not increased among users of low-dose combined COCs who are under 35 years old and do not smoke or have hypertension. ~~Women who have a history of stroke should not use COCs.~~

Draft Guidance Text, WARNINGS, Lines 366-370:

The likelihood of myocardial infarction (MI) is not increased among young women who use COCs and do not smoke or have hypertension or diabetes. Heavy smokers (≥ 15 cigs/day) older than 35 years should not take COCs. Women who currently have ischemic heart disease, or who have a history of this disease, should not use COCs due to an increased risk of MI and stroke.

Wyeth-Ayerst Comments: The deletion of the sentences “Heavy smokers older than 35...” and “women who currently have ischemic heart disease...” under this subsection of **WARNINGS** are consistent with our comments found on Pages 4 and 9 of this document.

Proposed Labeling:

The likelihood of myocardial infarction (MI) is not increased among young women who use COCs and do not smoke or have hypertension or diabetes. ~~Heavy smokers (≥ 15 eigs/day) older than 35 years should not take COCs. Women who currently have ischemic heart disease, or who have a history of this disease, should not use COCs due to an increased risk of MI and stroke.~~

**Draft Guidance Text, WARNINGS, Line 371:
Addition of Retinal vascular thrombosis subsection**

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the addition of a subsection entitled, "c. Retinal vascular thrombosis".

Proposed Labeling:

With use of COCs, there have been reports of retinal vascular thrombosis, which may lead to partial or complete loss of vision. If there are signs or symptoms such as visual changes, onset of proptosis or diplopia, papilledema, or retinal vascular lesions, the COC should be discontinued and the cause immediately evaluated.

References:

Appendix 12 contains copies of the following references to support our comments and proposed labeling.

- Jaais, F and Habib, ZA: Unilateral superior ophthalmic vein thrombosis in a user of oral contraceptives. Med J. Malaysia 49(4):416-418, 1994.
- Leong, KC and Tan, PL: Central retinal vein thrombosis in a woman on contraceptive pills. Singapore Med J 15(2): 156-157, 1974.
- Varga, M. recent experience on the ophthalmologic complications of oral contraceptives. Ann Ophthalmol 8(8): 925-934, 1976.

**Draft Guidance Text, WARNINGS, Line 372:
c. Valvular heart disease**

Wyeth-Ayerst Comments: The above-referenced subsection is re-lettered to be consistent with previous subsection changes made under the **Cardiovascular disease** section of **WARNINGS**.

Proposed Labeling:

c.d. Valvular heart disease

Draft Guidance Text, WARNINGS, Line 378

Draft Guidance Text, WARNINGS, Lines 385-399:

3. Carbohydrate metabolism

For women with diabetes (both insulin-dependent and non-insulin-dependent), who do not have vascular involvement, the advantages of COC use generally outweigh the risks, particularly in light of the risks associated with pregnancy in these women. The major concerns of COC use by this population are vascular disease and an added risk of thrombosis, although COC use by diabetic women appears to have only minimal effects on lipid metabolism and hemostasis. For diabetic women with nephropathy, retinopathy, neuropathy, or other vascular involvement, the risk-benefit ratio depends on the severity of the condition.

4. Lipid metabolism

Because some hyperlipidemias are risk factors for vascular disease, the appropriateness of COC use is dependent on the type and severity of known hyperlipidemias.

Wyeth-Ayerst Comments: Wyeth-Ayerst suggests moving the sections “**Carbohydrate metabolism**” and “**Lipid metabolism**” to **Cardiovascular Disease, WARNINGS** as these discussions pertain to vascular diseases. Wyeth-Ayerst also proposes to combine these sections and rename the new section, “**e. Diabetes and hyperlipidemia**”. Further, Wyeth-Ayerst proposes the addition of the sentence “COCs should not be used in women who have diabetes with vascular involvement (See **CONTRAINDICATIONS**)” to this section. Wyeth-Ayerst also suggests the deletion of “nephropathy, retinopathy,” and “or other vascular involvement” when assessing the risk-benefit ratio for diabetic women, as these conditions constitute vascular involvement and the use of COCs is contraindicated for these patients in the Draft Guidance.

Proposed Labeling:

~~3. Carbohydrate metabolism~~

~~4. Lipid metabolism~~

e. Diabetes and hyperlipidemia

COCs should not be used in women who have diabetes with vascular involvement (See **CONTRAINDICATIONS**). For women with diabetes (both insulin-dependent and non-insulin-dependent), who do not have vascular involvement, the advantages of COC use generally outweigh the risks, particularly in light of the risks associated with pregnancy in these women. The major concerns of COC use by this population are vascular disease and an added risk of thrombosis, although COC use by diabetic women appears to have only minimal effects on lipid metabolism and hemostasis. For diabetic women with ~~nephropathy, retinopathy, neuropathy, or other vascular involvement~~, the risk-benefit ratio depends on the severity of the condition.

Because some hyperlipidemias are risk factors for vascular disease, the appropriateness of COC use is dependent on the type and severity of the known hyperlipidemias.

Draft Guidance Text, WARNINGS, Line 378:

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the addition of a paragraph on minimizing a patient’s exposure to estrogen and progestin consistent with that in the 1994 COC Labeling Guidance. The paragraph is proposed as an addition to the **WARNINGS** before “**2. Elevated blood pressure**” and immediately following the proposed subsection “**e. Diabetes and hyperlipidemia.**” This section would read as follows.

“Minimizing exposure to estrogens and progestins is in keeping with good principles of therapeutics. For any particular estrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual patient. New acceptors of COCs should be started on preparations containing less than 50 mcg of estrogen.”

In support of the above-proposed labeling, Speroff et al, the editors of Clinical Gynecologic Endocrinology and Infertility (Sixth Edition), have stated that:

“The estrogen content (dosage) of the pill is of major importance. Thrombosis is one of the most serious side effects of the pill, playing a key role in the increased risk of death (in the past with high doses) from a variety of circulatory problems. This side effect is related to estrogen, and it is dose related. Therefore, the dose of estrogen is a critical issue in selecting an oral contraceptive.

As with the estrogen component, serious side effects have been related to the high doses of progestins used in old formulations, not the particular progestin, and routine use of oral contraceptives should now be limited to the low-dose products.

The therapeutic principle remains: utilize the formulations that give effective contraception and the greatest margin of safety. You and your patients are urged to choose a low-dose preparation containing less than 50 mcg of estrogen, combined with low doses of new or old progestins. Current data support the view that there is greater safety with preparations containing less than 50 mcg of estrogen. The arguments in this chapter indicate that all patients should begin oral contraception with low-dose products, and that patients on higher dose oral contraception should be changed to the low-dose preparations. Stepping down to a lower dose can be accomplished immediately with no adverse reactions such as increased bleeding or failure of contraception.”

Proposed Labeling:

Minimizing exposure to estrogens and progestins is in keeping with good principles of therapeutics. For any particular estrogen/progestin combination, the dosage regimen prescribed should be one which contains the least amount of estrogen and progestin that is compatible with a low failure rate and the needs of the individual patient. New acceptors of COCs should be started on preparations containing less than 50 ug of estrogen.

References:

Appendix 13 contains copies of the following references to support our comments and proposed labeling.

Speroff, L et al: Clinical Gynecologic Endocrinology and Infertility, Sixth Edition; C Mitchell, ed., (Baltimore, MD: Lippincott Williams & Wilkins, 1999), p. 873-874; 914.

Draft Guidance Text, WARNINGS, Lines 379-383:

2. Elevated blood pressure

For women with an elevation in blood pressure (160+/100+ mm/Hg), COC use would present an unacceptable health risk, and COCs should not be used. Similarly, hypertensive women with vascular disease should not use COCs.

Wyeth-Ayerst Comments: Wyeth-Ayerst is not aware of studies that stratified actual blood pressure values with increased risks of vascular events in users of COCs. Additionally, the risk of cardiovascular disease in patients with hypertension is determined not only by the level of blood pressure but also by the presence or absence of end-organ disease or other risk factors such as smoking, dyslipidemias, and diabetes.

The July 2000 ACOG Practice Bulletin entitled “The Use of Hormonal Contraception in Women with Coexisting Medical Conditions” states that women with well-controlled and monitored hypertension who are aged 35 years or younger are appropriate candidates for a trial of combination OCs formulated with 35 mcg or less of estrogen, provided they are otherwise healthy, show no evidence of end-organ vascular disease, and do not smoke cigarettes. If blood pressure remains well controlled with careful monitoring several months after initiating OCs, use can be continued.

Proposed Labeling:

2. Elevated blood pressure

For women with an elevation in blood pressure (160+/100+ mm/Hg), For women with uncontrolled hypertension, COC use would present an unacceptable health risk, and COCs should not be used. Similarly, hypertensive women with vascular disease should not use COCs. Increases in blood pressure have been reported in women taking COCs. In women with hypertension, a history of hypertension or hypertension-related diseases, including certain renal diseases, another method of contraception may be preferable. If COCs are used in such cases, close monitoring is recommended and, if a significant increase in blood pressure occurs, COCs should be discontinued.

References:

Appendix 4 contains copies of the following references to support our comments and proposed labeling.

- JNC VI, The sixth report of the Joint National Committee on the detection, evaluation, and treatment of high blood pressure. *Arch Intern Med* 157: 1997
- ACOG. The use of hormonal contraception in women with coexisting medical conditions. *ACOG Practice Bulletin*. 18: 2000.
- Knijff SCM, Goorissen EM, et al, editors. Summary of Contraindications to Oral Contraceptives. New York: Parthenon Publishing Group; 2000, 219-230.

Draft Guidance Text, WARNINGS, Lines 407 and 417:

- 5. Headaches**
- 6. Unexplained vaginal bleeding**

Wyeth-Ayerst Comments: The above-referenced sections on headaches and unexplained vaginal bleeding are renumbered to be consistent with previous changes made under WARNINGS.

Proposed Labeling:

- 35. Headaches**
- 46. Unexplained vaginal bleeding**

Draft Guidance Text, WARNINGS, Lines 428-443:

- 7. Breast cancer**

Although the risk of breast cancer may be slightly increased among current and recent users of COCs, this excess risk decreases over time after COC discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use, and no relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used COCs before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early COC use is extremely small.

Breast cancers diagnosed in current or previous OC users tend to be less invasive than in nonusers.

Women who currently have or have had breast cancer should not use COCs because breast cancer is a hormone-sensitive tumor.

Wyeth-Ayerst Comments: The results of a large reanalysis of 54 epidemiological studies, including data on 53,297 women with breast cancer and 100,239 women without breast cancer show a small increase in the risk (RR=1.24) of having breast cancer diagnosed during the use of combined oral contraceptives and in the ten years that follow. The risk disappears by ten years after stopping oral contraceptive use.

The Wyeth-Ayerst proposed wording more clearly defines the increased risk in terms of the detection of breast cancer. We believe that the Draft Guidance text discussing the risk of breast cancer should be qualified, otherwise, "risk" could be misinterpreted as an increased risk of the incidence of breast cancer versus an increase in the probability of detecting breast cancer.

Regarding the findings in women who first used COCs before age 20, further analysis noted "The estimated cumulative excess up to 10 years after stopping use in 10,000 women who used OCs from age 16-19 and from age 16-24 compared to never-users was 0.5 (SD 0.1) and 2.0 (SD 0.3), respectively." The Draft Guidance language does not adequately convey how small this excess risk is. Given the limitations of this study, this increased relative risk of breast cancer may not accurately identify the increase in attributable risk. A causal relationship has not been established. In addition, further conclusions noted, "It is not clear whether these findings are the consequence of cancers being diagnosed earlier in women who have used oral contraceptives, whether they are due to biological effects of the hormones, or whether they are due to a combination of both. Further research may clarify the mechanisms."

Therefore, Wyeth Ayerst proposes the following statements regarding oral contraceptive use and carcinoma of the breast which we believe discusses the "diagnosis" factor and other clinically relevant information covered in the above-referenced reanalysis.

Proposed Labeling:

57. Breast cancer

~~Although the risk of breast cancer may be slightly increased among current and recent users of COCs, this excess risk decreases over time after COC discontinuation and by 10 years after cessation the increased risk disappears. The risk does not increase with duration of use, and no relationships have been found with dose or type of steroid. The patterns of risk are also similar regardless of a woman's reproductive history or her family breast cancer history. The subgroup for whom risk has been found to be significantly elevated is women who first used COCs before age 20, but because breast cancer is so rare at these young ages, the number of cases attributable to this early COC use is extremely small.~~

~~Breast cancers diagnosed in current or previous OC users tend to be less invasive than in be less invasive than in nonusers.~~

~~Women who currently have or have had breast cancer should not use COCs because breast cancer is a hormone sensitive tumor.~~

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using combination oral contraceptives compared to never-users. The increased risk gradually

disappears during the course of the 10 years after cessation of combination oral contraceptive use. These studies do not provide evidence for causation. The observed pattern of increased risk of breast cancer diagnosis may be due to earlier detection of breast cancer in combination oral contraceptive users, the biological effects of combination oral contraceptives, or a combination of both. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent combination oral contraceptive users is small in relation to the lifetime risk of breast cancer. Breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

References:

Appendix 14 contains copies of the following references to support our comments and proposed labeling.

Collaborative Group on Hormonal Factors in Breast Cancer: Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *Lancet* 347: 1713-1727, 1996.

Collaborative Group on Hormonal Factors in Breast Cancer: Breast cancer and hormonal contraceptives: Further Results. *Contraception* 54: 1S-106S, 1996.

Draft Guidance Text, WARNINGS, Lines 445-449:

8. Cervical cancer

Some reports indicate a statistical association between COC use and cervical cancer, but several important methodological problems are inherent in studying this relationship, and the association remains unclear.

Wyeth-Ayerst Comments: A review of the published literature provides references (primary, meta-analysis, and review) describing a slightly increased risk of both squamous cell carcinoma and adenocarcinoma of the cervix.

Wyeth-Ayerst proposes the addition of the following text regarding cervical cancer and COC use to give prescribers additional clinically relevant information.

Proposed Labeling:

68. Cervical cancer

~~Some reports indicate a statistical association between COC use and cervical cancer, but several important methodological problems are inherent in studying this relationship, and the association remains unclear.~~ Some studies suggest that COC use has been associated with an increase in the risk of cervical intraepithelial neoplasia or invasive cervical cancer in some populations of women. However, there continues to be controversy about the extent to which such findings may be due to differences in sexual behavior and other factors. In cases of undiagnosed abnormal genital bleeding, adequate diagnostic measures are indicated.

References:

Appendix 15 contains copies of the following references to support our comments and proposed labeling.

Schlesselman JJ: Net effect of oral contraceptive use on the risk of cancer in women in the United States. *Obstet Gynecol* 85(5, Part 1): 793-801, 1995.

- Delgado-Rodriguez M et al: Oral contraceptives and cancer of the cervix uteri. A meta-analysis. *Acta Obstet Gynecol Scand* 71: 368-376, 1992.
- Ursin G et al: Oral contraceptive use and adenocarcinoma of cervix. *Lancet* 344: 1390-1394, 1994.
- WHO Collaborative Study of Neoplasia and Steroid Contraceptives: Invasive squamous-cell cervical carcinoma and combined oral contraceptives: Results from a multinational study. *Int J Cancer* 55: 228-236, 1993.

Draft Guidance Text, WARNINGS, Lines 451-458:

9. Gallbladder disease

COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

Women with a history of COC-related cholestasis are more likely to have the condition recur with subsequent COC use.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes relocating the subsection on "**Gallbladder Disease**" to **PRECAUTIONS**. This is based on recent data indicating that the risk of gallbladder disease is due to an acceleration of gallbladder disease in women predisposed to this condition. Thus, the overall risk of gallbladder disease is not increased, but is activated in women who are vulnerable because of asymptomatic disease or a tendency toward gallbladder disease. This is consistent with the wording proposed by the FDA. However, since this is a pre-existing condition that may be exacerbated by COCs and is relevant to a specific sub-population at risk, we believe it is more appropriate to address this condition in **PRECAUTIONS** (see Page 26 of this document for proposed labeling for **PRECAUTIONS, Gallbladder Disease.**)

Proposed Labeling:

9. Gallbladder disease

~~COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.~~

~~Women with a history of COC related cholestasis are more likely to have the condition recur with subsequent COC use.~~

References:

Appendix 21 contains a copy of references to support our comments and proposed labeling.

- WHO: Improving Access to Quality Care in Family Planning (1996). p 23.
- Rannevik, G et al: Effect of oral contraceptives on the liver in women with recurrent cholestasis (hepatosis) during previous pregnancies. *The Journal of Obstetrics and Gynaecology* 79: 1128-1136, 1972.
- Lindberg, MC: Hepatobiliary complications of oral contraceptives. *J Gen Interanat Med* 7: 199-209, 1992.
- Cohen, L et al: Pregnancy, oral contraceptives, and chronic familial jaundice with predominantly conjugated hyperbilirubinemia (Dubin-Johnson syndrome). *Gastroenterology* 62(6): 1182-1190, 1972.
- Drill, VA: Benign cholestatic jaundice of pregnancy and benign cholestatic jaundice from oral contraceptives. *Am J Obstet Gynecol* 119(2): 165-174, 1974.

Draft Guidance Text, WARNINGS, Lines 460-466:

10. Liver disease

Because steroid hormones are metabolized by the liver, women taking COCs may experience adverse hepatobiliary effects. Although case-control studies have indicated that the risk of both benign and malignant liver tumors may be slightly increased by COC use, the incidence of these tumors potentially attributable to COCs in the United States is minimal because the disease is very rare.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes to delete the term "slightly" used to describe the increased risk of both benign and malignant liver tumors. This is supported by at least one study that shows that the risk of developing hepatic adenomas is increased by a factor of nine for 13 to 36 months of COC use and by over 100 fold for use longer than 37 months. Additionally, the risk of hepatocellular carcinoma has been shown to be increased approximately 5 to 10 fold with COC use for more than 5 years. This increased risk is not consistent with the use of the term "slightly".

Wyeth-Ayerst also proposes the addition of the sentence "Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage" in this section. This is supported by several case reports of patients with benign hepatic adenomas presenting for medical care after rupture with massive intra-abdominal hemorrhage and hemodynamic instability. If not treated with immediate surgical resection of the ruptured adenoma these patients may die.

Proposed Labeling:

710. Liver disease

Because steroid hormones are metabolized by the liver, women taking COCs may experience adverse hepatobiliary effects. Although case-control studies have indicated that the risk of both benign and malignant liver tumors may be ~~slightly~~ increased by COC use, the incidence of these tumors potentially attributable to COCs in the United States is minimal because the disease is very rare. Rupture of hepatic adenomas may cause death through intra-abdominal hemorrhage.

References:

Appendix 16 contains copies of the following references to support our comments and proposed labeling.

- Rooks, J.B. et al. Epidemiology of hepatocellular adenoma. *JAMA* 242:644-648, 1979.
- Rosenberg, L. The risk of liver neoplasia in relation to combined oral contraceptives. *Contraception* 43: 643-652, 1991.
- Baum, JK. Et al. Possible association between benign hepatomas and oral contraceptives. *Lancet* 926-929, 1973.
- Bein, NN and Goldsmith HS. Recurrent massive hemorrhage from benign hepatic tumours secondary to oral contraceptives. *Br. J. Surg.* 64: 433-435, 1977.

Draft Guidance Text, WARNINGS, Line 468:

Women who currently have active liver disease should not use COCs.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes to delete the sentence "Women who currently have active liver disease should not use COCs." under **WARNINGS** consistent with the Wyeth-Ayerst comments found on Page 8 of this document.

Proposed Labeling:

~~Women who currently have active liver disease should not use COCs.~~

Draft Guidance Text, PRECAUTIONS, Lines 472-485:

1. Sexually transmitted diseases

Women should be informed that this product does not protect against infection from HIV (the virus that causes AIDS) or other sexually transmitted diseases (STDs), except symptomatic pelvic inflammatory disease. If a woman is at high risk for STDs, she should be encouraged to reduce risky behavior and to use condoms or other barrier methods in addition to COCs.

Clinically apparent pelvic inflammatory disease (PID) is less common in women taking COCs. Whether this reflects a protective or a masking effect of COCs is not known. COCs provide no protection against lower reproductive tract infection and appear to be associated with increased risk of infection with *Chlamydia trachomatis*. The risk of acquiring HIV infection in COC users is uncertain, with some studies showing an increased risk with COC use and others finding no association.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes deleting the term "high" in the second sentence on sexually transmitted diseases, as all women at risk for STDs should be encouraged to reduce risky behavior and use barrier methods to prevent STDs. As detailed in the 1998 Guidelines for STDs, preventing the spread of STDs requires that persons at risk for transmitting or acquiring infections change their behaviors.

With respect to the second paragraph, Wyeth-Ayerst proposes the addition of the sentence "There continues to be controversy about the extent to which such findings may be due to differences in sexual behavior or detection bias is uncertain." based on the support of the published literature. Bontis and colleagues detailed the prevalence of *C. trachomatis* infection in asymptomatic women of reproductive age and predicted subgroups at high and low risk of infection, with a minimum of laboratory tests. The report revealed that Chlamydia infection was associated with younger age, a history of PID, and more than four lifetime sexual partners. OC users had more infections than those women who used intrauterine devices, condoms, or no contraception. The authors concluded, "...*C. trachomatis* infection is associated with younger age, intense sexual life and use of oral contraceptives." Burkman reviewed hormonal effects on STDs and PID, and menstrual function and concluded that "There are several confusing issues regarding the relationship between OCs, sexually transmitted diseases, and PID. The use of OCs does not reduce the risk of gonococcal or chlamydial infection of the lower genital tract and in fact is associated with higher rates of detection of chlamydial infection. This latter finding may be the result of detection bias relative to OC users; in addition, data suggest that sex steroids may enhance the spread of these infections."

Proposed Labeling:

1. Sexually transmitted diseases

Women should be informed that this product does not protect against infection from HIV (the virus that causes AIDS) or other sexually transmitted diseases (STDs), except symptomatic pelvic inflammatory disease. If a woman is at high risk for STDs she should be encouraged to reduce risky behavior and to use condoms or other barrier methods in addition to COCs.

Clinically apparent pelvic inflammatory disease (PID) is less common in women taking COCs. Whether this reflects a protective or a masking effect of COCs is not known. COCs provide no protection against lower reproductive tract infection and appear to be associated with increased risk of infection with *Chlamydia trachomatis*. The risk of acquiring HIV infection in COC users is uncertain, with some studies showing an increased risk with COC use and others finding no association. There continues to be controversy about the extent to which such findings may be due to detection bias or differences in sexual behavior between OC users and non-OC users.

References:

Appendix 17 contains copies of the following references to support our comments and proposed labeling.

1998 Guidelines for Treatment of Sexually Transmitted Diseases. *MMWR* 47(No. RR-1): 1-8, 1998.

Bontis, J et al: Detection of chlamydia trachomatis in asymptomatic women: relationship to history, contraception, and cervicitis. *Advances in Contraception* 10(4): 309-15, 1994.

Burkman, RT: Noncontraceptive effects of hormonal contraceptives: bone mass, sexually transmitted disease and pelvic inflammatory disease, cardiovascular disease, menstrual function, and future fertility. *Am J of Obstet & Gynecol* 170 (5 Pt. 2): 1569-75, 1994.

Draft Guidance Text, PRECAUTIONS, Lines 487-492:

2. Physical examination and follow-up

Before initiating COC use, blood pressure should be measured and details of the woman's personal and family medical history should be obtained. Blood pressure should be measured periodically during COC use and additional clinical evaluation should be based on these initial and follow-up findings.

Wyeth-Ayerst Comments: The 1994 COC Labeling Guidance describes that a periodic history and physical examination is appropriate for all women, including women using oral contraceptives. The physical examination, however, may be deferred until after the initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician. The physical examination should include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests. Wyeth-Ayerst proposes the addition of "a complete physical examination" to the above-referenced section.

In support of Wyeth-Ayerst's proposal, Speroff et al, the editors of Clinical Gynecologic Endocrinology and Infertility (Sixth Edition), have stated that:

"In view of the increased safety of low-dose preparations for healthy young women with no risk factors, such patients need be seen only every 12 months for exclusion of problems by history, measurement of the blood pressure, urinalysis, breast examination, palpation of the liver, and pelvic examination with Pap smear.

Proposed Labeling:

2. Physical examination and follow-up

Before initiating COC use, a complete physical examination, including blood pressure should be measured taken and details of the woman's personal and family medical history should be obtained. ~~Blood pressure~~ Such medical examinations should be measured-performed periodically during COC use and additional clinical evaluation should be based on these initial and follow-up findings.

References:

Appendix 18 contains copies of the following references to support our comments and proposed labeling.

Speroff, L et al: Clinical Gynecologic Endocrinology and Infertility, Sixth Edition; C Mitchell, ed., (Baltimore, MD: Lippincott Williams & Wilkins, 1999), p. 913.

Draft Guidance Text, PRECAUTIONS, Line 493:

Addition of Carbohydrate and lipid metabolism

Wyeth-Ayerst Comments: Studies have demonstrated that high dose OC's may impair glucose tolerance (increase plasma levels of insulin and blood glucose). Therefore, women with glucose intolerance or diabetes may require careful monitoring.

Oral contraceptives have been associated with acute pancreatitis in women with pre-existing hyperlipidemia. However, it has been reported in women, without a history of this condition, using oral contraceptives. Since oral contraceptives have been shown to increase fasting triglycerides 13-75%, there may be an association between an increase in triglycerides and pancreatitis.

Based on the literature reviewed and receipt of spontaneous reports of pancreatitis in women with or without hyperlipidemia, Wyeth-Ayerst proposes the following subsection entitled **Carbohydrate and lipid metabolism** be added to the **PRECAUTIONS** section.

Proposed Labeling:

3. Carbohydrate and lipid metabolism

COCs may cause glucose intolerance. Women with impaired glucose tolerance or diabetes mellitus should be carefully monitored.

Persistent hypertriglyceridemia may occur in a small proportion of COC users.

In patients with familial defects of lipoprotein metabolism receiving estrogen-containing preparations, there have been reports of significant elevations of plasma triglycerides leading to pancreatitis.

Women who are being treated for hyperlipidemias should be followed closely if they elect to use COCs.

References:

Appendix 19 contains copies of the following references to support our comments and proposed labeling.

- Bergholm U, Langman M, Rawlins, M., et al. Drug-induced acute pancreatitis. *Pharmacoepidemiology and Drug Safety* 4: 1995, 329-34.
- Liu, JW. Birth control pills and pancreatitis. *MD State Med J* 2: 1982, 66-67.
- Parker, WA. Estrogen-induced pancreatitis. *Clinical Pharmacy* 2: 1983, 75-79.
- Bank S, Marks IN. Hyperlipaemic pancreatitis and the pill. *Postgraduate Medical Journal* 46: 1960, 576-588.
- Wynn V, Doar JW, Mills GL. Some effects of oral contraceptives on serum lipid and lipoprotein levels. *Lancet* 2: 1966, 720-723. [Erratum, *Lancet* 2: 1966, 799.]
- Godsland IAF, Crook D, Simpson R, et al. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. *NEJM* 323:20; 1990, 1375-1381.
- Vaziri SM, Evans JC, Larson MG, et al. The impact of female hormone usage on the lipid profile. *Arch Intern Med* 153: 1993, 2200-2206.
- Watanabe Rm, Azen CG, Roy S, et al. Defects in carbohydrate metabolism in oral contraceptive users without apparent metabolic risk factors. *J Clin Endocrinol Metab* 79: 1994, 1277-83.
- Godsland IAF, Crook D, Simpson R, et al. The effects of different formulations of oral contraceptive agents on lipid and carbohydrate metabolism. *NEJM* 323:20; 1990, 1375-1381.
- Sheu W H-H, HSU C-H, Chen Y-S, et al. Prospective evaluation of insulin resistance and lipid metabolism in women receiving oral contraceptives. *Clin Endocrinol* 40: 1994, 249-255.
- Speroff L, Glass RH, Kase NG. Oral Contraception (in) Clinical Gynecologic Endocrinology and Infertility: 5th Ed.: 1994; Williams & Wilkins, Ed., 727.
- Betschart J. Oral contraception and adolescent women with insulin-dependent diabetes mellitus: risks, benefits and implications for practice. *Diabetes Educator* 22(4): 1996, 374-378.

Draft Guidance Text, PRECAUTIONS, Relocation of "Gallbladder disease" from WARNINGS:

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes relocating "Gallbladder disease" to **PRECAUTIONS**. This proposal is based on recent data indicating that the risk of gallbladder disease is due to an acceleration of gallbladder disease in women predisposed to this condition. Thus, the overall risk of gallbladder disease is not increased but is activated in women who are vulnerable because of asymptomatic disease or a tendency toward gallbladder disease. This is consistent with the wording proposed by the FDA. However, since this is a pre-existing condition that may be exacerbated by COCs and is relevant to a specific sub-population at risk, we believe it is more appropriate to address this condition in **PRECAUTIONS**, please see Wyeth-Ayerst comments on Page 21 of this document.

A large number of international agencies and organizations active in the area of family planning policies and programs in collaboration with the WHO program area of Family Reproductive Health has established medical eligibility criteria for initiating and continuing COC use. Wyeth-Ayerst is in agreement with the WHO recommendations which state that in patients with a history of pregnancy-related cholestasis, COCs may generally be used. History of pregnancy-related cholestasis may predict an increased risk of developing COC-associated cholestasis.

Proposed Labeling:

4. Gallbladder disease

COCs may worsen existing gallbladder disease and may accelerate the development of this disease in previously asymptomatic women.

Women with a history of COC-related cholestasis or women who develop cholestasis during pregnancy are likely to have the condition recur with subsequent COC use.

References:

Appendix 20 contains copies of the following references to support our comments and proposed labeling.

- WHO: Improving Access to Quality Care in Family Planning (1996), p 23.
- Rannevik, G et al: Effect of oral contraceptives on the liver in women with recurrent cholestasis (hepatosis) during previous pregnancies. *The Journal of Obstetrics and Gynaecology* 79: 1128-1136, 1972.
- Lindberg, MC: Hepatobiliary complications of oral contraceptives. *J Gen Interanat Med* 7: 199-209, 1992.
- Cohen, L et al: Pregnancy, oral contraceptives, and chronic familial jaundice with predominantly conjugated hyperbilirubinemia (Dubin-Johnson syndrome). *Gastroenterology* 62(6): 1182-1190, 1972.
- Drill, VA: Benign cholestatic jaundice of pregnancy and benign cholestatic jaundice from oral contraceptives. *Am J Obstet Gynecol* 119(2): 165-174, 1974.

Draft Guidance Text, PRECAUTIONS, Line 494-526:

3. Drug Interactions

The efficacy of COCs is reduced by hepatic enzyme-inducing drugs such as the antituberculosis drug rifampin and the anticonvulsants phenytoin, carbamazepine, and barbiturates. The efficacy of COCs when used with griseofulvin may also be reduced.

The following section contains information on drug interactions with ethinyl estradiol-containing products that have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens.

- a. The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbital, phenytoin, and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol-containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduce the plasma concentrations of ethinyl estradiol by 30 percent.

Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl estradiol-containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increase AUC values for ethinyl estradiol by 20 percent.

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

- b. Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Wyeth-Ayerst Comments: We suggest that the following text from the Draft Guidance Drug Interactions Section be amended.

In addition to the hepatic enzyme inducing drugs listed by FDA, Wyeth-Ayerst proposes adding the following drugs: "ritonavir", "some other protease inhibitors", "phenylbutazone", "topiramate", "modafinil", "penicillins", and "tetracyclines". Wyeth-Ayerst also proposes the addition of St. John's wort (*hypericum perforatum*). There have been published reports of breakthrough bleeding in women taking COCs and St. John's wort concomitantly. St. John's wort may induce hepatic microsomal enzymes, leading to a possible decrease in ethinyl estradiol concentration and a theoretical reduced efficacy of COCs. Although a causal relationship has not been established Wyeth-Ayerst believes it is appropriate to inform users of such a risk.

Since the substances mentioned above may lead to decreased hormonal plasma concentrations, Wyeth-Ayerst suggests the addition of information advising that patients use a non-hormonal back-up method of contraception during concomitant use and following discontinuation of these substances.

Wyeth-Ayerst also proposes the addition troleandomycin. Troleandomycin is marketed in the United States by Pfizer Inc under the registered trademark of TAO. As noted in Pfizer's current direction circular, "the administration of troleandomycin has been associated with an allergic type of cholestatic hepatitis. Troleandomycin should be administered with caution to patients concurrently receiving estrogen containing oral contraceptives." Upon review of 46 cases presented in the published literature discussing cholestatic jaundice coincident with the combined intake of combined oral contraceptives (COCs) and troleandomycin, Wyeth-Ayerst concurs with Pfizer's labeling for troleandomycin.

Per the above discussed recommendations, Wyeth-Ayerst proposes the following text revision to the Drug Interactions Section under **PRECAUTIONS**:

Proposed Labeling:

5.3. Drug Interactions

~~The efficacy of COCs is reduced by hepatic enzyme inducing drugs such as the antituberculosis drug rifampin and the anticonvulsants phenytoin, carbamazepine, and barbiturates. The efficacy of COCs when used with griseofulvin may also be reduced.~~

The following section contains information on drug interactions with ethinyl estradiol-containing products that have been reported in the public literature. It is unknown whether such interactions occur with drug products containing other types of estrogens.

- ~~a. The metabolism of ethinyl estradiol is increased by rifampin and anticonvulsants such as phenobarbital, phenytoin, and carbamazepine. Coadministration of troglitazone and certain ethinyl estradiol-containing drug products (e.g., oral contraceptives containing ethinyl estradiol) reduce the plasma concentrations of ethinyl estradiol by 30 percent.~~

~~Ascorbic acid and acetaminophen may increase AUC and/or plasma concentrations of ethinyl estradiol. Coadministration of atorvastatin and certain ethinyl estradiol-containing drug products (e.g., oral contraceptives containing ethinyl estradiol) increase AUC values for ethinyl estradiol by 20 percent.~~

Clinical pharmacokinetic studies have not demonstrated any consistent effect of antibiotics (other than rifampin) on plasma concentrations of synthetic steroids.

- b. Drug products containing ethinyl estradiol may inhibit the metabolism of other compounds. Increased plasma concentrations of cyclosporin, prednisolone, and theophylline have been reported with concomitant administration of certain drugs containing ethinyl estradiol (e.g., oral contraceptives containing ethinyl estradiol). In addition, drugs containing ethinyl estradiol may induce the conjugation of other compounds.

Decreased EE plasma concentrations may cause an increased incidence of breakthrough bleeding and menstrual irregularities and may possibly reduce efficacy of the COC.

Reduction of EE concentrations have been reported with substances that induce hepatic microsomal enzymes. Examples of such substances are rifampin, barbiturates, phenylbutazone, phenytoin, carbamazepine, griseofulvin, topiramate, some protease inhibitors, modafinil and possibly ritonavir and St. John's wort.

Substances that may decrease plasma EE concentrations by other mechanisms include any substance that reduces gut transit time and certain antibiotics (e.g., ampicillin and other penicillins, tetracyclines), by a decrease of enterohepatic circulation of estrogens.

During concomitant use of EE containing products and substances that may lead to decreased plasma steroid hormone concentrations, it is recommended that a nonhormonal back-up method of birth control (such as condoms and spermicide) be used in addition to the regular intake of "TRADENAME". If use of the substance is required for a prolonged period of time, COCs should not be considered the primary contraceptive.

After discontinuation of substances that may lead to decreased EE plasma concentrations, use of a nonhormonal back-up method is recommended for 7 days. Longer use of a back-up method is advisable after discontinuation of substances that have led to induction of hepatic microsomal enzymes, resulting in decreased EE plasma concentrations. It may sometimes take several weeks until enzyme induction has completely subsided, depending on dosage, duration of use and rate of elimination of the inducing substance.

Some substances may increase plasma EE concentrations. These include:

- Competitive inhibitors for sulfation in the gastrointestinal wall, such as ascorbic acid (vitamin C) and acetaminophen. Sulfation of EE occurs in the gastrointestinal wall.
- Substances that inhibit cytochrome P 450 3A4 isoenzymes such as indinavir, fluconazole and troleandomycin. Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs.
- Atovastatin (unknown mechanism)

EE may interfere with the metabolism of other drugs by inhibiting hepatic microsomal enzymes, or by inducing hepatic drug conjugation, particularly glucuronidation. Accordingly, plasma and tissue concentrations may either be increased (e.g., cyclosporine, theophylline, corticosteroids) or decreased.

The prescribing information of concomitant medications should be consulted to identify potential interactions.

References:

Appendix 21 contains copies of the following references to support our comments and proposed labeling.

- Sinofsky FE and Pasquale SA: The effect of fluconazole on circulating ethinyl estradiol levels in women taking oral contraceptives. *Am J Obstet Gynecol* 178(2): 300-304, 1998.
- Baciewicz, AM and Self, TH: Rifampin drug interactions. *Arch Intern Med* 144: 1667-1671, 1984.
- Joshi, JV et al: A study of interaction of a low-dose combination oral contraceptive with anti-tubercular drugs. *Contraception* 21(6): 617-629, 1980.
- Gupta, KC and Ali, MY: Failure of oral contraceptive with rifampin. *Medical Journal of Zambia* 15(1): 23, 1980.
- Back, DJ et al: The interaction of phenobarbital and other anticonvulsants with oral contraceptive steroid therapy. *Contraception* 22(5): 495-503, 1980.
- Mattson, RH et al: Use of oral contraceptives by women with epilepsy. *JAMA* 256(2): 238-240, 1986.
- Crawford, P et al: The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. *Br J Clin Pharmacol* 30: 892-896, 1990.
- Côté, J: Interaction of griseofulvin and oral contraceptives. *Journal of the American Academy of Dermatology* 22(1): 124-125, 1990.
- McDaniel, PA and Caldrony, RD: Oral contraceptives and griseofulvin interaction. *Drug Intelligence and Clinical Pharmacy* 20: 384, 1986.
- van Dijke, CPH and Weber, JCP: Interaction between oral contraceptives and griseofulvin. *BMJ* 288: 1125-1126, 1984.
- Back, DJ et al: Evaluation of Committee on Safety of Medicines yellow card reports on oral contraceptive-drug interactions with anticonvulsants and antibiotics. *Br J Clin Pharmacol* 25: 527-532, 1988.
- Rosenfeld, WE et al: Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. *Epilepsia* 38(3): 317-323, 1997.
- Perucca, E and Bialer, J: The clinical pharmacokinetics of the newer antiepileptic drugs. Focus on topiramate, zonisamide and tiagabine. *Clin Pharmacokinet* 31(1): 29-46, 1996.
- McDonald, CK and Gerber, J: Caveats when using non-nucleosides and protease inhibitors. Avoiding drug interactions with antiretroviral agents (part 2). *The Journal of Respiratory Diseases* 19(2): 103-113, 1998.
- Flexner, C: HIV-protease inhibitors. *Drug Therapy* 338(18): 1281-1292, 1998.
- Kakuda, TN et al: Protease inhibitors for the treatment of human immunodeficiency virus infection. *Am J Health-Syst Pharm* 55: 233-254, 1998.
- Lin-in Tseng, A and Foisy, MM: Management of drug interactions in patients with HIV. *The Annals of Pharmacotherapy* 31: 1040-1058, 1997.
- Viracept (nelfinavir mesylate) Oral Powder current prescribing information. (in) Physicians' Desk Reference (www.pdrel.com); 1-17, 9/25/00.
- Silber, TJ: Apparent oral contraceptive failure associated with antibiotic administration. *Journal of Adolescent Health Care* 4(4): 287-289, 1983.
- Bacon, JF and Shenfield, GM: Pregnancy attributable to interaction between tetracycline and oral contraceptives. *BMJ*: February 2, 1980, 293.
- Bainton, R: Interaction between antibiotic therapy and contraceptive medication. *Oral Surg Oral Med Oral Pathol* 61: 453-455, 1986.
- Dossetor, J: Drug interactions with oral contraceptives. *BMJ*: November 22, 1975: 467.
- Nager, C and Murphy AA: Antibiotics and oral contraceptive pills. *Seminar Reprod Endocrinol* 7(3): 220-223, 1989.
- Qin-Ying Y, Bergquist C, Gerden B. The safety of St. John's wort [letter]. *Lancet* 2000; 355:576577.
- Kerb R et al. Urinary 6 β -hydroxycortisol excretion rate is affected by treatment with hypericum extract. *Eur J Clin Pharmacol* 1999; 55: A22 (abstr).
- Nebel A et al. Potential metabolic interaction between St. John's wort and theophylline. *Ann Pharmacother* 1999; 33: 502
- Modafinil Prescribing Information, January, 1999.
- Fevry J, Van Steenberghe W, Desmet V, Deruyttere M, De Groote J: Severe intrahepatic cholestasis due to the combined intake of oral contraceptives and triacetyloleandomycin. *Acta Clin Belg* 38: 242-245, 1983.
- Miguet JP, Vuitton D, Allemand H, Pessayre D, Monange C, Hirsch JP, et al: An outbreak of jaundice due to the combination troleandomycin - oral contraceptives. *Gastroenterol Clin Biol* 4: 420-4, 1980.
- Haber I and Hubens H: Cholestatic jaundice after triacetyloleandomycin and oral contraceptives. The diagnostic value of gamma-glutamyl transpeptidase. *Acta Gastroenterol Belg* 43: 475-482, 1980.

Claudel S, Euvrard P, Bory R, Chavaillon A, Paliard P: Intrahepatic cholestasis following combination of triacetyloleandomycin-estrogen/progestogens. *Nouv Presse Med* 8: 1182, 1979.
TAO[®] (troleandomycin) prescribing information (In) *Physicians' Desk Reference*, 54th Edition. (Montvale, NJ: Medical Economics Company, 2000), 2370.
Royal College of General Practitioners' Oral Contraception Study. Oral contraceptives and gallbladder disease. *Lancet* 2: 1982, 957.

Draft Guidance Text, PRECAUTIONS, Line 528, 550:

4. Interactions that affect laboratory tests

5. Carcinogenesis

Wyeth-Ayerst Comments: The above-referenced sections are renumbered to be consistent with previous section changes made under **PRECAUTIONS**.

Proposed Labeling:

64. Interactions that affect laboratory tests

75. Carcinogenesis

Draft Guidance Text, PRECAUTIONS, Line 553:

Addition of Depression subsection

Wyeth-Ayerst Comments: The 1994 COC Labeling Guidance describes that patients becoming significantly depressed while taking oral contraceptives should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug related. Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Wyeth-Ayerst is in agreement with the 1994 COC Labeling Guidance and requests that the FDA give due consideration in reinstating this particular precaution in the draft COC guidance for industry.

Furthermore, several clinical studies and a review article, based largely on COCs containing greater than 35 mcg ethinyl estradiol, suggest that the incidence of depression is higher in women who use COCs and that depression may recur in women taking COCs who have a history of depression.

Wyeth-Ayerst proposes adding **Depression** to the **PRECAUTIONS** section of the Draft COC Labeling Guidance.

Proposed Labeling:

8. Depression

Women with a history of depression should be carefully observed and the drug discontinued if depression recurs to a serious degree. Patients becoming significantly depressed while taking COCs should stop the medication and use an alternate method of contraception in an attempt to determine whether the symptom is drug-related.

References:

Appendix 22 contains copies of the following references to support or comments and proposed labeling.

Herzberg, BN et al: Oral contraceptives, depression, and libido. *BMJ*: 495-500, 1971.

Cullberg J: Mood changes and menstrual symptoms with different gestagen/estrogen combinations. *Acta Psychiatr Scand (Suppl)*: 236, 1972.

Slap, GB: Oral contraceptives and depression. *J of Adolescent Health Care* 2: 53-64, 1981.

Draft Guidance Text, PRECAUTIONS, Line 558:

6. Pregnancy

Wyeth-Ayerst Comments: The above-referenced section is renumbered to be consistent with previous section changes made under **PRECAUTIONS**.

Proposed Labeling:

26. Pregnancy

Draft Guidance Text, PRECAUTIONS, Lines 564-571:

7. Nursing mothers

COCs given in the postpartum period may interfere with lactation by decreasing the quantity of breast milk and by affecting its composition. Oral contraceptive steroids have been reported in the milk of breast-feeding mothers with no apparent clinical significance; long-term follow-up of children whose mothers used COCs while breast-feeding has shown no deleterious effects. However, women who are fully breast-feeding should not start taking COCs until 6 weeks postpartum.

Wyeth-Ayerst Comments: The 1994 COC Labeling Guidance describes that small amounts of oral-contraceptive steroids have been identified in the milk of nursing mothers, and a few adverse effects on the child have been reported, including jaundice and breast enlargement. In addition, oral contraceptives given in the postpartum period may interfere with lactation by decreasing the quantity and quality of breast milk. There are non-hormonal as well as non-estrogen containing contraceptives available that may be utilized for safe and effective contraception until the nursing mother has weaned her child. Furthermore, a large number of international agencies and organizations active in the area of family planning policies and programs in collaboration with the World Health Organization (WHO) program area of Family Reproductive Health have established medical eligibility criteria for initiating and continuing COC use. As stated by the WHO, there is some theoretical concern that the neonate may be at risk due to exposure to steroid hormones.

The authors of Drugs in Pregnancy and Lactation summarized, "Use of oral contraceptives during lactation has been associated with shortened duration of lactation, decreased infant weight gain, decreased milk production, and decreased composition of nitrogen and protein content of milk. Although the magnitude of these changes is low, the changes in milk production and composition may be of nutritional importance in malnourished mothers." Therefore, Wyeth-Ayerst recommends changes to this section to reflect the potential for adverse effects.

Proposed Labeling:

107. Nursing mothers

COCs given in the postpartum period may interfere with lactation by decreasing the quantity of breast milk and by affecting its composition. Oral contraceptive steroids have been reported in the milk of breast-feeding mothers and a few adverse effects on the child have

been reported, including jaundice and breast enlargement with no apparent clinical significance; long-term follow-up of children whose mothers used COCs while breast-feeding has shown no deleterious effects. However, women who are fully breastfeeding should not start taking COCs until 6 weeks postpartum. The use of COCs is generally not recommended until the nursing mother has completely weaned her child.

References:

Appendix 23 contains copies of the following references to support our comments and proposed labeling.

- WHO: Improving Access to Quality Care in Family Planning (1996), p. 13.
Briggs, GG et al: Drugs in Pregnancy and Lactation. CW Mitchell, Ed., (Williams & Wilkins, Baltimore, MD, 1994), pp. 644-647.
WHO Task Force on Oral Contraceptives. Effects of hormonal contraceptives on milk volume and infant growth. *Contraception* 30: 505-521, 1984.
WHO Task Force on Oral Contraceptives, Special Programme of Research, Development, and Research Training in Human Reproduction. Effects of hormonal contraceptives on breast milk composition and infant growth. *Studies in Family Planning* 19(6): 361-369, 1988.

Draft Guidance Text, PRECAUTIONS, Line 573, 578, 584:

8. Fertility following discontinuation

9. Pediatric use

10. Information for the patient

Wyeth-Ayerst Comments: The above-referenced sections are renumbered to be consistent with previous changes made under **PRECAUTIONS**.

Proposed Labeling:

118. Fertility following discontinuation

129. Pediatric use

1310. Information for the patient

Draft Guidance Text, ADVERSE EXPERIENCES, Lines 607-619:

Less frequently, the following adverse reactions may occur:

- Vomiting and other gastrointestinal symptoms (e.g., bloating)
- Mood changes and depression
- Decreased libido
- Acne
- Dizziness
- Weight gain (or loss)
- Melasma
- Increased cervical ectopia
- Vaginal candidiasis
- Fluid retention
- Ocular effects, including decreased tolerability to contact lenses

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the following additions and deletions to **ADVERSE EXPERIENCES** based upon our spontaneous reporting database and information available in the published literature.

Proposed Labeling:

Less frequently, the following adverse reactions may occur:

- Vomiting and other gastrointestinal symptoms (e.g., bloating, pain, or cramps)
- Breast pain, secretion, or enlargement
- Mood changes, and depression, and nervousness
- Decreased Changes in libido
- Acne
- Dizziness
- Changes in ~~W~~weight or appetite (increase or decrease)gain (or loss)
- Melasma
- Increased cervical ectopia
- Vaginal candidiasis
- Fluid retention
- Ocular effects, including decreased tolerability to contact lenses
- Anaphylactic/oid reactions, including rash, urticaria, shock, and angioedema
- Erythema nodosum
- Erythema multiforme
- Hirsutism
- Alopecia
- Optic neuritis
- Dysmenorrhea
- Hemolytic uremic syndrome
- Exacerbation of systemic lupus erythematosus
- Aggravation of varicose veins
- Exacerbation of porphyria
- Exacerbation of chorea

References:

Appendix 24 contains copies of the following references to support our comments and proposed labeling.

- Hauglustaine, D et al: Recurrent hemolytic uremic syndrome during oral contraception. *Clin Nephrol* 15(3): 148-153, 1981.
- Schillinger, F et al: Hemolytic uremic syndrome (HUS) in a patient on oral contraceptives. *Kidney International* 29: 777, 1986.
- Hoorntje, S et al: Reversal of long-standing renal insufficiency by captopril in a patient with relapsing hemolytic uremic syndrome due to an oral contraceptive. *Ann Intern Med* 94(3): 355-357, 1981.
- Urbanek, RW and Cohen, DJ: Porphyria cutanea tarda: pregnancy versus estrogen effect. *J Am Acad Dermatol* 31(2 Pt 2): 390-392, 1994.
- Willerson, D et al: Familial porphyria cutanea tarda in a patient with retinitis pigmentosa. *Ann Ophthalmol* 11(3): 409-411, 1979.
- Kansky, A et al: Oral contraceptives and their influence on porphyrin concentrations in erythrocytes and urine. *Dermatologica* 157: 181-185, 1978.
- Roberts, DT et al: Hereditary coproporphyrin presenting with photosensitivity induced by the contraceptive pill. *Br J Dermatol* 96: 549-554, 1977.
- Nausieda PA et al: Chorea induced by oral contraceptives. *Neurology* 29: 1605-1609, 1979.
- Omdal, R and Roalso, S: Chorea gravidarum and chorea associated with oral contraceptives - diseases due to antiphospholipid antibodies? *Acta Neurol Scand* 86: 219-220, 1992.
- Dove DJ: Chorea associated with oral contraceptive therapy. *Am J Obstet Gynecol* 137(6): 740-741, 1980.
- Buyon JP et al: Can women with SLE safely use exogenous estrogens? *J Clin Rheumatol* 1(4): 205-212, 1995.

- Jungers, P et al: Influence of oral contraceptive therapy on the activity of SLE. *Arthritis Rheum* 25(6): 618-623, 1982.
- Todd, GR et al: Pulmonary hypertension, SLE, and the contraceptive pill. *Ann Rheum Dis* 44: 266-267, 1985.
- Miller MH: Pulmonary hypertension, SLE, and the contraceptive pill: another report. *Ann Rheum Dis* 46: 159-161, 1987.
- Vin F et al: Influence of estrogens and progesterone on the venous system of the lower limbs in women. *J Dermatol Surg Oncol* 18(10): 888-892, 1992.
- Bye PGT et al: Clinical assessment of a low-oestrogen combined oral contraceptive. *BMJ* 2: 389-392, 1973.

Draft Guidance Text, ADVERSE EXPERIENCES, Line 620:

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes to add depressed folate levels to this section since it is of importance to the prescribing physician. Although folate levels are not routinely tested, the physician should be aware of this effect of COCs if such a level is tested. Occasional reports of megaloblastic anemia, which results from folate deficiency, have been reported in COC users. Additionally, the prescriber should be aware of the decrease in folate levels seen in women taking COCs should the woman become pregnant shortly after discontinuing the medication. Since pregnant women are prone to develop folate deficiency, women who become pregnant shortly after cessation of COCs may have increased risk of developing folate deficiency and its complications.

Proposed Labeling:

Serum folate levels may be depressed by COC therapy. This may be of clinical significance if a woman becomes pregnant shortly after discontinuing COCs.

References:

Appendix 25 contains copies of the following references to support our comments and proposed labeling.

- Stegers-Theunissen RPM et al: Sub-50 oral contraceptives affect folate kinetics. *Gynecol Obstet Invest* 36(4): 230-233, 1993.
- Grace E et al: Hematologic abnormalities in adolescents who take oral contraceptive pills. *J Pediatrics* 101(5): 771-774, 1982.
- Martinez O and Roe DA: Effect of oral contraceptives on blood folate levels in pregnancy. *Am J Obstet Gynecol* 128(3): 255-261, 1977.
- Shojania AM: Oral contraceptives: effect on folate and vitamin B12 metabolism. *Can Med Assoc J* 126(3): 244-247, 1982.

Draft Guidance Text, ADVERSE EXPERIENCES, Lines 625-629:

Some COC users have breakthrough bleeding or spotting, although this side effect generally improves over time. Breakthrough bleeding is somewhat more likely to occur following a missed pill. More rarely, prolonged bleeding or amenorrhea can occur. However, most women experience beneficial changes in menstrual cycle patterns (see **NONCONTRACEPTIVE HEALTH BENEFITS**).

Wyeth-Ayerst Comments: Since COCs may mask pre-existing amenorrhea. Wyeth-Ayerst proposes to add the following sentence: "Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent."

Proposed Labeling:

Some COC users have breakthrough bleeding or spotting, although this side effect generally improves over time. Breakthrough bleeding is somewhat more likely to occur following a missed pill. More rarely, prolonged bleeding or amenorrhea can occur. Some women may encounter post-pill amenorrhea or oligomenorrhea, especially when such a condition was preexistent. However, most women experience beneficial changes in menstrual cycle patterns (see **NONCONTRACEPTIVE HEALTH BENEFITS**).

Draft Guidance Text, NONCONTRACEPTIVE HEALTH BENEFITS, Lines 658-660:

- Decreased incidence of endometrial cancer
- Decreased incidence of ovarian cancer
- Decreased incidence of benign breast tumors

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes adding the following noncontraceptive health benefit to the above section of the draft COC guidance for industry: Preservation of bone mineral density.

Wyeth-Ayerst requests that the FDA give due consideration to the following scientific justification supporting preservation of bone mineral density (BMD) as a benefit of COCs.

Shargil evaluated the use of a triphasic COC in women who experienced symptoms of estrogen deficiency during perimenopause. In this three year prospective study, 200 perimenopausal women from 41 to 49 years of age who were suffering from menopausal symptoms, but were still menstruating, were evaluated. One group of women (n=100) received a low-dose triphasic Levonorgestrel/EE COC which was selected to provide both contraception and hormone replacement therapy (HRT). Another group (n=100) served as non-hormonal controls. Both groups were studied prior to initiation of treatment and at three- or six-month intervals for a total of three years. The bone mass results of this study demonstrated the following: "At the beginning of the study, both groups had normal bone mass. At six months, there was still no significant difference between the groups. At one year and thereafter, the controls lost bone and were losing bone mass at a rate of about 2% per year. At three years the controls showed a loss of about 6% of bone mass compared with pretreatment levels. In contrast, the low dose triphasic COC group did not experience loss of bone during the 3-year study." Shargil stated, "...the beneficial effect of HRT on bone preservation is substantial."

In a cross-sectional retrospective epidemiologic study, Kleerekoper and colleagues evaluated the association of oral contraceptive (OC) use with BMD in 681 women (15-91 years of age). Ever-users of OCs were significantly less likely to have a low BMD measurement (odds ratio=0.35, 95% confidence interval (CI)=0.23 to 0.53), and significantly more likely to have a high BMD measurement (OR, 2.19; 95% CI, 1.70 to 2.83). These results were further confirmed by controlling for other variables (such as age, menopausal status, term pregnancies) in a logistic regression procedure. History of OC use (ever, never) and duration of use (by 5-year increments) were significantly and positively correlated with BMD (OR, 0.78; 95% CI, 0.63 to 0.98 and OR, 0.83, 95% CI, 0.71 to 0.98, respectively). The authors concluded, "...premenopausal OC use is advantageous to skeletal health not only during the reproductive years, but also lasting into the postmenopausal period. A logical extension of our findings is that premenopausal OC use would be associated with a diminished likelihood of developing postmenopausal osteoporosis and fracture occurrence."

Additionally, DeCherney reported that a number of studies provide evidence of an association between OC use and increased bone mineral density. He concluded, "Although a specific oral contraceptive formulation cannot be recommended at this time, it is clear that an estrogen dose of 20 to 35 mcg combined with a progestin may offer the best bone-sparing effects while minimizing the thrombotic risks of oral contraceptives."

Proposed Labeling:

- Decreased incidence of endometrial cancer
- Decreased incidence of ovarian cancer
- Decreased incidence of benign breast tumors
- Preservation of bone mineral density

References:

Appendix 26 contains copies of the following references to support our comments and proposed labeling.

Shargil, AA: Hormone replacement therapy in perimenopausal women with a triphasic contraceptive compound: a three-year prospective study. *Int J Fertil* 30(1): 15-28, 1985.

Kleerekoper, M et al: Oral contraceptive use may protect against low bone mass. *Arch Intern Med* 151: 1971-1976, 1991.

DeCherney, A: Bone-sparing properties of oral contraceptives. *Am J Obstet Gynecol* 174: 15-20, 1996.

Draft Guidance Text, DOSAGE AND ADMINISTRATION, Lines 669-673:

To achieve maximum contraceptive effectiveness, COCs must be taken as directed. One tablet is to be taken every day, preferably at the same time. Single missed pills should be taken as soon as remembered. If 2 or more pills are missed, backup contraception should be used until pills have been taken for 7 consecutive days. For more specific instructions, see **INSTRUCTIONS FOR USE**.

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the addition of the word "active" for clarification.

Proposed Labeling:

To achieve maximum contraceptive effectiveness, COCs must be taken as directed. One tablet is to be taken every day, preferably at the same time. Single missed pills should be taken as soon as remembered. If 2 or more pills are missed, backup contraception should be used until active pills have been taken for 7 consecutive days. For more specific instructions, see **INSTRUCTIONS FOR USE**.

II. PATIENT LABELING (INSTRUCTIONS FOR USE)

Draft Guidance Text, HOW TO TAKE THE PILL, Lines 715-719:

Check the picture of the pill pack below for:

- Which pill to take first
- The direction in which to take the pills
- The week numbers and pill colors

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the addition of “day or” for clarification as not all pill packs have week numbers.

Proposed Labeling:

Check the picture of the pill pack below for:

- Which pill to take first
- The direction in which to take the pills
- The day or week numbers and pill colors

Draft Guidance Text, WHEN TO START YOUR FIRST PACK OF PILLS, Lines 807-810:

After a miscarriage or abortion, you can start taking the pill right away if the miscarriage or abortion occurred less than 20 weeks (or halfway) into the pregnancy. If the miscarriage or abortion occurred after 20 weeks, consult your **clinician or health care professional about when to start taking the pill.**

Wyeth-Ayerst Comments: The literature supports the use of COC’s immediately after a first trimester abortion. Speroff et al, the editors of Clinical Gynecologic Endocrinology and Infertility (Sixth Edition), have also stated that: “After termination of a pregnancy of less than 12 weeks, oral contraception can be started immediately.” In addition, Dorland’s Illustrated Medical Dictionary (27th Edition) defined trimester as a period of 3 months. Wyeth-Ayerst proposes that this time period be stated in language more understandable to the lay public.

Proposed Labeling:

After a miscarriage or abortion, you can start taking the pill right way if the miscarriage or abortion occurred ~~less than 20 weeks (or halfway) into~~ during the first three months of the pregnancy. If the miscarriage or abortion occurred after ~~20 weeks~~ three months, consult your clinician or healthcare professional about when to start taking the pill.

References:

Appendix 27 contains copies of the following references to support our comments and proposed labeling.

- Dorland’s Illustrated Medical Dictionary, 27th Edition; (Philadelphia, PA: W.B. Saunders Company, Inc., 1988), p. 1758.
- Speroff, L et al: Clinical Gynecologic Endocrinology and Infertility, Sixth Edition; C Mitchell, ed., (Baltimore, MD: Lippincott Williams & Wilkins, 1999), p. 909.
- Dahlman, T et al: Changes in blood coagulation and fibrinolysis in the normal puerperium. *Gynecol Obstet Invest* 20(1): 37-44, 1985.
- Gray, RH et al: Postpartum return to ovarian activity in nonbreastfeeding women monitored by urinary assays. *J Clin Endocrin Metabol* 64(4): 645-650, 1987.
- Hatherley, LI: Lactation and postpartum infertility: the use-effectiveness of natural family planning (NFP) after term pregnancy. *Clin Reprod Fertil* 3(4): 319-334, 1985.

Draft Guidance Text, IF YOU’VE JUST HAD A BABY, Lines 814-825:

If you are fully breast-feeding (not giving your baby any other source of milk or not giving your baby any food or formula), wait to start taking combined pills until your baby is at least 6 weeks old or until your menstrual periods begin, whichever comes first. The pills may slightly

reduce your breast milk supply. You should start your pills by 6 months, even if you haven't yet had a menstrual period.

If you are partially breast-feeding (giving your baby some food or formula), begin taking your pills when you begin giving your baby other formula or foods. Check with your healthcare provider if you have not had a menstrual period.

If you are not breast-feeding, you can start taking your pills 2-3 weeks after the delivery of your baby.

Wyeth-Ayerst Comments: Wyeth-Ayerst's proposed revisions to the **PATIENT LABELING (INSTRUCTIONS FOR USE)** regarding breastfeeding that are consistent with the proposed changes to **WARNINGS** for post-partum use of oral contraceptives and **PRECAUTIONS** for women who are breastfeeding.

Proposed Labeling:

~~If you are fully breast-feeding (not giving your baby any other source of milk or not giving your baby any food or formula), wait to start taking combined pills until your baby is at least 6 weeks old or until your menstrual periods begin, whichever comes first. The pills may slightly reduce your breast milk supply. You should start your pills by 6 months, even if you haven't yet had a menstrual period.~~

~~If you are partially breast-feeding (giving your baby some food or formula), begin taking your pills when you begin giving your baby other formula or foods. Check with your healthcare provider if you have not had a menstrual period.~~

If you are breast-feeding, do not take COCs until you have completely weaned your child.

If you are not breast-feeding, you can start taking your pills 2-3 weeks after the delivery of your baby.

Draft Guidance Text, MISSED PILLS, Line 884:

Wyeth-Ayerst Comments: Wyeth-Ayerst proposes the addition of patient instructions for missing two or three consecutive active pills. This is consistent with the 1994 COC Labeling Guidance.

Proposed Labeling:

If you miss *two or more* [color(s)] hormonal pills in a row during the third week of pill use (21-day or 28-day pack) or if you miss *three or more* [color(s)] hormonal pills in a row during the first three weeks:

- *Most important: Use backup birth control (such as condoms) until you have been back on the hormonal pills for 7 days in a row.*
- Day 1 starters should throw out the rest of the pack and start a new pack that same day.
- Sunday starters should keep taking one tablet every day until Sunday; on Sunday, throw out the rest of the pack and start a new pack that same day.
- You may not have a withdrawal bleed until the end of the second pack. If you do not have a withdrawal bleed at the end of the second pack, call your health-care professional or clinic for a pregnancy test.

Draft Guidance Text IF YOU HAVE SEVERE VOMITING, Lines 907-910:

IF YOU HAVE SEVERE VOMITING within 3 hours of taking your pill, it may not work as well. Take a second pill. If you vomit more than once, it may be safest to use a backup method for the next 7 days. Call your healthcare professional or clinic for further advice.

Wyeth-Ayerst Comments: The 1994 COC Labeling Guidance describes other gastrointestinal events, such as vomiting, that can interfere with hormone absorption. In addition, the 1994 COC Labeling Guidance notes some medications, such as antibiotics that may interfere with hormone absorption. Wyeth-Ayerst continues to be in agreement with the 1994 COC Labeling Guidance and requests that the FDA retain this information in the Draft Guidance.

Further, Sparrow et al studied recognized factors associated with pill method failure, including nausea and vomiting. The authors evaluated 163 cases of pill failure (pregnancy) in patients who had never taken their pills more than 12 hours late. The authors reported that "Vomiting only was associated with 14 failures (9%). Diarrhoea only was associated with 23 failures (14%). Diarrhoea and vomiting was associated with 19 failures (12%). The total number of failures associated with vomiting and/or diarrhoea was 56 (34%)." When this study was extended for 3 more years and 137 additional cases were evaluated, the authors reported 63 additional cases of pill failure associated with vomiting and/or diarrhea (46%). Based on these findings, Sparrow et al recommended abstinence or use of a barrier back-up method of contraception for 7 days when vomiting occurs within 3 hours of taking the pill or if diarrhea lasts for 12 or more hours.

In another study of pregnancies associated with pill failure, Kovacs et al concluded that malabsorption as a result of vomiting or diarrhea was one of the most common causes of pill failure. The authors reported that diarrhea and vomiting were associated with pill failure in 56 of the 209 women evaluated (26.8%). Therefore, Kovacs et al recommended that "...additional contraceptive precautions be taken until at least seven continuous tablets have been taken after an episode which may impair the efficacy of the Pill."

Based on this information, Wyeth-Ayerst proposes the following changes to the guidance text.

Proposed Labeling:

IF YOU HAVE SEVERE VOMITING within 3 hours of taking your pill, it may not work as well. Take a second pill. If you vomit more than once, it may be safest to use a backup method for the next 7 days. Diarrhea may increase gastrointestinal motility and reduce hormone absorption. Call your healthcare professional or clinic for further advice.

References:

Appendix 28 contains copies of the following reference to support our comments and proposed labeling.

Sparrow, MJ: Pill method failures. *N Z Med J* 100(818): 102-105, 1987.

Sparrow, MJ: Pregnancies in reliable pill takers. *N Z Med J* 102(879): 575-577, 1989.

Kovacs, GT et al: Inadvertent pregnancies in oral contraceptive users. *Med J Aust* 150(10): 549-51, 1989.