NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice of opportunity for hearing shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk (address given below) during working hours, Monday through Friday.

Communications forwarded in response to this notice should be identified with the reference number DESI 2238, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852.

Supplements (identify with NDA number):

Hydrocortisone products—Division of Oncology and Radiopharmaceutical Drug Products, (HFD–150), Rm. 17B–45, Bureau of Drugs.

Negatol or hexetidine products—Division of Anti-Infective Drug Products, (HFD–140), Rm. 12B–45, Bureau of Drugs.

Estrogen products—Division of Metabolism and Endocrine Drug Products, (HFD–130), Rm. 14B–04, Bureau of Drugs.

Original abbreviated new drug applications (identify as such): Division of Generic Drug Monographs (HFD–530), Bureau of Drugs.

Request for Hearing (identify with Docket number appearing in the heading of this notice): Hearing Clerk, Food and Drug Administration (HFC–20), Rm. 4–65.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Documents Center (HFC–18), Rm. 4–62.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD–101), Bureau of Drugs.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.31) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: September 17, 1976.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc.76–28434 Filed 9–28–76;8:45 am]

[Docket No. 76N–0377; DESI 7661]

CERTAIN DRUGS CONTAINING FLUOXYMESTERONE AND ETHINYL ESTRADIOL; DIETHYLSTILBESTROL AND METHYLTESTOSTERONE; CHLOROTRIANISENE AND METHYLTESTOSTERONE; OR TESTOSTERONE ENANTHATE AND ESTRADIOL VALERATE

Drugs for Human Use; Drug Efficacy Study Implementation; Followup Notice and Opportunity for Hearing

The Food and Drug Administration is reclassifying the less-than-effective indications for certain estrogen-androgen combination drugs, offering an opportunity for a hearing on the reclassification, and announcing the conditions under which the drugs may be marketed for the indications for which they continue to be regarded as effective. Persons who wish to request a hearing may do so on or before October 29, 1976.

In a notice (DESI 7661; Docket No. FDC–D–313 (now Docket No. 76N–0377)) published in the FEDERAL REGISTER of September 8, 1972 (37 FR 18225), the Food and Drug Administration announced its conclusions that the drug products described below are: (1) effective for the prevention of postpartum breast engorgement and for the menopausal syndrome in those patients not improved by estrogen alone; (2) probably effective for the treatment of postmenopausal and senile osteoporosis when used in conjunction with other important therapeutic measures such as diet, calcium physiotherapy, and good general health promoting measures; (3) possibly effective for use in osteoporosis in certain patients following long-term adrenocortical therapy; prevention of postpartum breast manifestations of lactation; protein depletion and chronic debility; tissue atrophy in geriatric patients; depletion of protein and osseous tissues during corticosteroid therapy, spinal paraplegia, and delayed fracture union; and for dysmenorrhea; and (4) lacking substantial evidence of effective for male climacterium. The notice also offered an opportunity for a hearing concerning the indication concluded at that time to lack substantial evidence of effectiveness. No person has submitted any data in support of the probably and possibly effective indications, and those indications are now reclassified as lacking substantial evidence of effectiveness.

The notice that follows does not pertain to the indication stated in the notice of September 8, 1972, to lack substantial evidence of effectiveness. No person requested a hearing concerning it, and it is no longer allowable in labeling. Any such product labeled for that indication is subject to regulatory action.

1. NDA 11–267; Halodrin Tablets containing fluoxymesterone and ethinyl estradiol; The Upjohn Co., 7171 Portage Rd., Kalamazo, MI 49002.

2. NDA 8–099; Tylosterone Injecton; and

3. NDA 7–661; Tylosterone Tablets each containing diethylstilbestrol and methyltestosterone; Eli Lilly & Co., P.O. Box 618, Indianapolis, IN 46206.

4. NDA 10–597; Tace with Androgen Capsules containing chlorotrianisene and methyltestosterone; Merrell-National Laboratories Division of Richardson-Merrell, Inc., P.O. Box 15260, Cincinnati, OH 45215.

5. NDA 9–545; Deladumone Injection and Deladumone OB Injection each containing testosterone enanthate and estradiol valerate; Squibb Pharmaceutical Co., Division of E. R. Squibb & Sons, Inc., P.O. Box 4000, Princeton, NJ 08540.

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. An approved new drug application is a requirement for marketing such drug products.

In addition to the holder(s) of the new drug application(s) specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved new drug application, that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufacturers or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD–310), 5600 Fishers Lane, Rockville, MD 20852.

A. *Effectiveness classification.* The Food and Drug Administration has reviewed all available evidence and concludes that the drugs are effective for the indications listed in the labeling conditions below. These indications have been reworded to coincide with the physician labeling for estrogens for general use published elsewhere in this issue of the FEDERAL REGISTER. (See discussion in B.2.c.) The drugs now lack substantial evidence of effectiveness for the indications evaluated as probably and possibly effective in the September 8, 1972 notice.

B. *Conditions for approval and marketing.* The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* Testosterone enanthate with estradiol valerate is in sterile solution form suitable for parenteral administration. Methyltestosterone with

diethylstilbestrol is in sterile solution form suitable for parenteral administration or in appropriate dosage form for oral administration. The other drugs are in a dosage form suitable for oral administration.

2. *Labeling conditions.* a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drugs are labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The Indications are as follows:

Postpartum breast engorgement. Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

Moderate to severe *vasomotor* symptoms associated with the menopause in those patients not improved by estrogen alone. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)

The dosages for any of these indications which are to be used in labeling must be supported by clinical data if the indication was not included in the labeling which the Academy reviewed for that particular drug.

c. The Food and Drug Administration has undertaken a comprehensive review of the estrogen class of drugs, particularly their indications and certain adverse effects which recent papers in the scientific literature have reported to be associated with the use of estrogens. As a result of this review, the Food and Drug Administration concludes that there is a need (1) for extensive revision of the physician labeling for this class of drugs and (2) for patient package labeling. Such labeling has been developed for the use of manufacturers, repackers, relabelers, and distributors of estrogens for general use and is published elsewhere in this issue of the FEDERAL REGISTER. It will be updated as necessary.

Therefore, published elsewhere in this issue of the FEDERAL REGISTER are the following: (1) A notice entitled "Physician Labeling and Patient Labeling for Estrogens for General Use" setting forth physician labeling text and proposed patient labeling for estrogens. (Docket No. 76N-0381.) (2) A notice of proposed rule making entitled "Estrogens for General Use; Proposed Requirement for Labeling Directed to the Patient" to establish a requirement for patient package labeling for drug products containing estrogens. (Docket No. 76N-0384.)

Because of the wide use of these drugs and thus the general interest of not only manufacturers and physicians but of consumers also, the impact the new labeling may have on future uses of estrogens, and the new information on which the labeling changes are based, the Food and Drug Administration has determined that opportunity should be offered to all interested persons to comment on the text of both the physician labeling and the proposed patient labeling. Although the physician labeling is to be put into use as set forth in item 3 below, comments will be reviewed for appropriate change.

Upon review of the comments and promulgation of a final regulation requiring patient package labeling, a followup DESI notice, applying to DESI drugs and all other estrogens not specifically excepted, will be published in the FEDERAL REGISTER giving the text of current physician labeling, if it is revised on the basis of comments, and the text of current patient labeling. In the meantime, use of the physician labeling set forth in Docket No. 76N-0381 is required and use of the patient labeling set forth there is encouraged.

3. *Marketing status.* a. Marketing of such drug products that are now the subject of an approved or effective new drug application may be continued provided that on or before November 29, 1976, the holder of the application submits the following if he has not previously done so:

(i) A supplement to provide updating information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)) to the extent required in abbreviated applications (21 CFR 314.1 (f)), except that for conjugated estrogen preparations and estradiol valerate sterile oleaginous solution, full manufacturing information shall be submitted.

(ii) A supplement to provide for revised physician labeling in accord with the indications stated above in item B.2.b. of this notice and substantially the same in content as the physician labeling set forth in the notice entitled "Physician Labeling and Patient Labeling for Estrogens for General Use" published elsewhere in this issue of the FEDERAL REGISTER (Docket No. 76N-0381).

b. Because of the importance of the revised labeling information and the need for its prompt dissemination, the Food and Drug Administration will regard as misbranded and subject to regulatory action, any estrogen product that is covered by this notice and shipped in interstate commerce by a manufacturer, repacker, relabeler, or distributor after November 29, 1976, without labeling which is substantially the same in content as the physician labeling set forth in the notice entitled "Physician Labeling and Patient Labeling for Estrogens for General Use" (Docket No. 76N-0381), published elsewhere in this issue of the FEDERAL REGISTER, and in accord with the indications set forth in item B.2.b. of this notice. Such labeling may be put into use in advance of approval or submission of a supplement to a new drug application. If a hearing has been requested on the question of effectiveness of a specific product (see Item C below), that product will not be regarded as misbranded if its labeling is otherwise revised as stated above but retains the indication on which the hearing is requested.

c. Approval of an abbreviated new drug application must be obtained prior to marketing such product. The application shall contain the information specified in 21 CFR 314.1(f). Marketing prior to approval of a new drug application will subject such products, and those persons who caused the products to be marketed, to regulatory action.

C. *Notice of opportunity for hearing.* On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111 (a)(5), and 21 CFR 300.50, demonstrating the effectiveness of the drug(s) for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice.

Notice is given to the holder(s) of the new drug application(s), and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) and all amendments and supplements thereto providing for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice on the ground that new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug product(s) will have all the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. An order withdrawing approval will not issue with respect to any application(s) supplemented, in accord with this notice, to delete the claim(s) lacking substantial evidence of effectiveness.

In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201 (p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reason.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Parts 310, 314), the applicant(s)

and all other persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named above (21 CFR 310.6), are hereby given an opportunity for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products.

If an applicant or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file (1) on or before October 29, 1976, a written notice of appearance and request for hearing, and (2) on or before November 29, 1976, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of such drug product. Any such drug product labeled for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice of opportunity for hearing shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk (address given below) during working hours, Monday through Friday.

Communications forwarded in response to this notice should be identified with the reference number DESI 7661, directed to the attention of the appropriate officer named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852.

Supplements (identify with NDA number): Division of Metabolism and Endocrine Drug Products (HFD–130), Rm. 14B–03, Bureau of Drugs.

Original abbreviated new drug applications (identify as such): Division of Generic Drug Monographs (HFD–530), Bureau of Drugs.

Request for Hearing (identify with Docket number appearing in the heading of this notice): Hearing Clerk, Food and Drug Administration (HFC–20), Rm. 4–65.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Document Center (HFC–18), Rm. 4–62.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD–101), Bureau of Drugs.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.31) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: September 17, 1976.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc.76–28435 Filed 9–28–76;8:45 am]

[Docket No. 76N–0356; DESI 1543]

CERTAIN ESTROGEN-CONTAINING DRUGS FOR ORAL OR PARENTERAL USE

Drugs for Human Use; Drug Efficacy Study Implementation; Followup Notice and Opportunity for Hearing

The Food and Drug Administration is reclassifying the less-than-effective indications for certain estrogen drugs, offering an opportunity for a hearing on the reclassification, and announcing the conditions under which the drugs may be marketed for the indications for which they continue to be regarded as effective. Persons who wish to request a hearing may do so on or before October 29, 1976.

In a notice (DESI 1543; Docket No. FDC–D–405 (now Docket No. 76N–0356)) published in the FEDERAL REGISTER of July 25, 1972 (37 FR 14826), the Food and Drug Administration announced its conclusions that the drug products described below are effective, probably effective, possibly effective, and lacking substantial evidence of effectiveness for their various labeled indications. The notice provided an opportunity for a hearing for the indications concluded at that time to lack substantial evidence of effectiveness. With one exception, no data in support of any of the less-than-effective indications were submitted. The exception concerned the tablet form of Premarin (NDA 4–782), for which data were submitted in support of the probably effective indication for use in selected cases of osteoporosis. The data have been reviewed and determined not to provide substantial evidence of effectiveness. A notice will be published later in the FEDERAL REGISTER setting forth an analysis of the data and reasons for this conclusion. The date of that notice will be the basis of determining the date hearing requests may be submitted for Premarin Tablets only for that indication. Except for the opportunity for a hearing on the effectiveness of Premarin Tablets for osteoporosis, this product is affected by the conclusions of this notice. All less-than-effective indications are now reclassified as lacking substantial evidence of effectiveness.

The notice that follows does not pertain to the indications stated in the notice of July 25, 1972, to lack substantial evidence of effectiveness. No person requested a hearing concerning them, and they are no longer allowable in the labeling. Any such product labeled for those indications is subject to regulatory action.

These drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. An approved new drug application is a requirement for marketing such drug products.

I. SHORT-ACTING ESTROGENS

1. NDA 0–740; Ovocylin Dipropionate Injection containing estradiol dipropionate; Ciba Pharmaceutical Co., Division of Ciba-Geigy Corp., 556 Morris Ave., Summit, NJ 07901.

2. NDA 1–543; Estrugenone Suspension containing estrone; Kremers-Urban Co., P.O. Box 2038, Milwaukee, WI 53201.

3. NDA 3–977; Theelin Aqueous Suspension containing estrone; Parke, Davis & Co., G.P.O. Box 118, Detroit, MI 48232.

4. NDA 4–823; Estrone Aqueous Suspension containing estrone; Abbott Laboratories, Abbott Park, 14th & Sheridan Rd., North Chicago, IL 60064.

5. NDA 5–292; Estinyl Tablets containing ethinyl estradiol; Schering Corp., Galloping Hill Rd., Kenilworth, NJ 07033.

6. NDA 5–490; Lynoral Tablets containing ethinyl estradiol; Organon, Inc., Division of Akzona, Inc., 375 Mt. Pleasant Ave., West Orange, NJ 07052.

7. NDA 8–759; Vallestril Tablets containing methallenestril; G. D. Searle & Co., P.O. Box 5110, Chicago, IL 60680.

8. NDA 4–782; Permarin Tablets; and

9. NDA 10–402; Premarin Intravenous, each containing conjugated estrogens; Ayerst Laboratories, Division American Home Products Corp., 685 Third Ave., New York, NY 10017.

The following short-acting estrogen was not included in the July 25, 1972 notice but is affected by this notice: NDA 16–649; Feminone Tablets containing ethinyl estradiol; The Upjohn

Co., 7171 Portage Rd., Kalamazoo, MI 49002.

II. LONH-ACTING ESTROGENS

1. NDA 8-102; Tace 12 mg Capsules; and

2. NDA 11-444; Tace 25 mg Capsules each containing chlorotrianisene; Merrell-National Laboratories, Division Richardson-Merrell, Inc., P.O. Box 15260, Cincinnati, OH 45215.

3. NDA 9-402; Delestrogen Sterile Oleauginous Solution containing estradiol valerate; Squibbs Pharmaceutical Co., E. R. Squibb & Sons, Inc., Box 4000, Princeton, NJ 08540.

4. NDA 10-753; Estradurin Sterile Powder for Injection containing polyestradiol phosphate; Ayerst Laboratories.

The following long-acting estrogen was not included in the July 25, 1973 notice but is affected by this notice: NDA 16-235; Tace 72 mg Capsules containing chlorotrianisene; Merrell-National Laboratories.

III. SCOPE OF NOTICE

In addition to the holder(s) of the new drug application(s) specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject of an approved new drug application, that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD-310), 5600 Fishers Lane, Rockville, MD 20852.

IV. CLASSIFICATION AND MARKETING CONDITIONS

A. *Effectiveness classification.* 1. The Food and Drug Administration has reviewed all available evidence and concludes that the drugs are effective for the indications listed in the labeling conditions below. These indications have been reworded to coincide with the physician labeling published elsewhere in this issue of the FEDERAL REGISTER (See discussion in B.2.c.). The drugs now lack substantial evidence of effectiveness for the indications evaluated as probably and possibly effective in the July 25, 1972 notice.

2. The National Academy of Sciences-National Research Council considered the indication, abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, to be effective. As stated, however, the indication is deficient in that it does not consider necessary prior diagnostic steps or the use of a progestational agent simultaneously or in sequence. Although the July 25, 1972 notice classified this indication as effective, the Director of the Bureau of Drugs has concluded that while estrogens may have a use in some cases of dysfunction uterine bleeding, the above indication is inadequate, incomplete, and not appropriate in labeling. Therefore, it is not included in the indications listed in the labeling conditions.

B. *Conditions for approval and marketing.* The Food and Drug Administration is prepared to approve new drug applications and supplements to previously approved new drug applications under conditions described herein.

1. *Form of drug.* a. Short-Acting Estrogens. Estradiol dipropionate, estrone, and conjugated estrogens are in a form suitable for parenteral administration. Ethinyl estradiol, methallenestril, and conjugated estrogens are in tablet form suitable for oral administration.

b. Long-Acting Estrogens. Chlorotrianisene is in capsule form suitable for oral administration. Estradiol valerate is in sterile oleaginous solution and polyestradiol phosphate is in sterile dry powder form both suitable for parenteral administration.

2. *Labeling conditions.* a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drug is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The Indications are as follows for both the short-acting and long-acting estrogens:

Moderate to severe *vasomotor* symptoms associated with the menopause (there is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause and they should not be used to treat these conditions).

Female hypogonadism.

Female castration.

Primary ovarian failure.

Postpartum breast engorgement—although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

The following indications may be included provided the recommended dosage schedules of the preparation are consistent with those recommended by the Academy:

Atrophic vaginitis.

Kraurosis vulvae.

Prostatic carcinoma—palliative therapy of advanced disease.

Additional indication for short-acting estrogens—breast cancer (for palliation only) in appropriately selected women, such as those who are more than 5 years post-menopausal with progressing inoperable or radiation-resistant disease, and in men with inoperable disease in whom bilateral orchidectomy is contraindicated.

The dosages for any of these indications that are to be used in labeling must be supported by clinical data if the indication was not included in the labeling which the Academy reviewed for that particular drug.

c. The Food and Drug Administration has undertaken a comprehensive review of the estrogen class of drugs, particularly their indications and certain adverse effects which recent papers in the scientific literature have reported to be associated with the use of estrogens. As a result of this review, the Food and Drug Administration concludes that there is a need (1) for extensive revision of the physician labeling for this class of drugs and (2) for patient package labeling. Such labeling has been developed for the use of manufacturers, repackers, relabelers, and distributors of estrogens for general use and is published elsewhere in this issue of the FEDERAL REGISTER. It will be updated as necessary.

Therefore, published elsewhere in this issue of the FEDERAL REGISTER are the following: (1) A notice entitled "Physician Labeling and Patient Labeling for Estrogens for General Use" setting forth physician labeling text and proposed patient labeling for estrogens. (Docket No. 76N-0381.) (2) A notice of proposed rule making entitled "Estrogens for General Use; Proposed Requirement for Labeling Directed to the Patient" to establish a requirement for patient package labeling for drug products containing estrogens. (Docket No. 76N-0384.)

Because of the wide use of these drugs and thus the general interest of not only manufacturers and physicians but of consumers also, the impact the new labeling may have on future uses of estrogens, and the new information on which the labeling changes are based, the Food and Drug Administration has determined that opportunity should be offered to all interested persons to comment on the text of both the physician labeling and the proposed patient labeling. Although the physician labeling is to be put into use as set forth in item 3 below, comments will be reviewed for appropriate change.

Upon review of the comments and promulgation of a final regulation requiring patient package labeling, a followup DESI notice, applying to DESI drugs and all other estrogens not specifically excepted, will be published in the FEDERAL REGISTER giving the text of current physician labeling, if it is revised on the basis of comments, and the text of current patient labeling. In the meantime, use of the physician labeling set forth in Docket No. 76N-0381 is required and use of the patient labeling set forth there is encouraged.

3. *Marketing status.* a. Marketing of such drug products that are now the subject of an approved or effective new drug application may be continued provided that on or before November 29, 1976, the holder of the application submits the following if he has not previously done so:

(1) A supplement to provide updating information with respect to items 6

(components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD–356H (21 CFR 314.1(c)) to the extent required in abbreviated applications (21 CFR 314.1(f)), except that for conjugated estrogen preparations and estradiol valerate sterile oleaginous solution, full manufacturing information shall be submitted.

(ii) A supplement to provide for revised physician labeling in accord with the indications stated above in item B.2.b. of this notice and substantially the same in content as the physician labeling set forth in the notice entitled "Physician Labeling and Patient Labeling for Estrogens for General Use" published elsewhere in this issue of the FEDERAL REGISTER (Docket No. 76N–0381).

b. Because of the importance of the revised labeling information and the need for its prompt dissemination, the Food and Drug Administration will regard as misbranded and subject to regulatory action, any estrogen product that is covered by this notice and shipped in interstate commerce by a manufacturer, repacker, relabeler, or distributor after November 29, 1976 without labeling which is substantially the same in content as the physician labeling set forth in the notice entitled "Physician Labeling and Patient Labeling for Estrogens for General Use" (Docket No. 76N–0381), published elsewhere in this issue of the FEDERAL REGISTER, and in accord with the indications set forth in item B.2.b. of this notice. Such labeling may be put into use in advance of approval or submission of a supplement to a new drug application. If a hearing has been requested on the question of effectiveness of a specific product (see Item C below), that product will not be regarded as misbranded if its labeling is otherwise revised as stated above but retains the indication on which the hearing is requested.

c. (i) Approval of abbreviated new drug application must be obtained prior to marketing any such product except estradiol valerate sterile oleaginous solution. The abbreviated application shall contain the information specified in 21 CFR 314.1(f), except that applications for conjugated estrogens shall include full manufacturing information as required by items 7 (composition) and 8 (methods, facilities, and controls) of the new drug application form FD–356H (21 CFR 314.1(c)).

(ii) For estradiol valerate sterile oleaginous solution, approval of a full new drug application (21 CFR 314.1(c)(2)) must be obtained prior to marketing such product.

d. Marketing prior to approval of a new drug application will subject such products, and those persons who caused the products to be marketed, to regulatory action.

C. *Notice of opportunity for hearing.* On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111 (a)(5), demonstrating the effectiveness of the drug(s) for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice.

Notice is given to the holder(s) of the new drug application(s), and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) and all amendments and supplements thereto providing for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice on the ground that new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug product(s) will have all the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. An order withdrawing approval will not issue with respect to any application(s) supplemented, in accord with this notice, to delete the claim(s) lacking substantial evidence of effectiveness.

In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201 (p) of the act, or pursuant to section 107 (c) of the Drug Amendments of 1962; or for any other reason.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Parts 310, 314), the applicant(s) and all other persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named above (21 CFR 310.6), are hereby given an opportunity for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products. The opportunity for a hearing does not apply at this time to Premarin Tablets for the indication osteoporosis for reasons discussed above.

If an applicant or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file (1) on or before October 29, 1976, a written notice of appearance and request for hearing, and (2) on or before November 29, 1976, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of such drug product. Any such drug product labeled for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice of opportunity for hearing shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk (address given below) during working hours, Monday through Friday.

Communications forwarded in response to this notice should be identified with the reference number DESI 1543, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852.

Supplements (identify with NDA number): Division of Metabolic and Endocrine Drug Products (HFD–130), Rm. 14B–03, Bureau of Drugs.

Original abbreviated new drug applications (identify as such): Division of Generic Drug Monographs (HFD–530), Bureau of Drugs.

Request for Hearing (identify with Docket number appearing in the heading of this notice): Hearing Clerk, Food and Drug Administration (HFC–20), Rm. 4–65.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Document Center (HFC–18), Rm. 4–62.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD–101), Bureau of Drugs.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.31) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: September 17, 1976.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc.76–28436 Filed 9–28–76;8:45 am]

[Docket No. 76N–0381; DESI No's. 740, 1543, 2238, and 7661]

PHYSICIAN LABELING AND PATIENT LABELING FOR ESTROGENS FOR GENERAL USE

Drugs for Human Use; Drug Efficacy Study Implementation

The Food and Drug Administration (FDA) is providing revised physician labeling as a guide for manufacturers and distributors of estrogenic drug products for general use and seeking comments on patient labeling for those drugs. Many of those products have been reviewed as part of the Drug Efficacy Study. The need for revised physician labeling and available patient labeling arises principally from reports which associate an increased risk of adverse effects with the use of estrogens. Interested persons are invited to comment on the patient labeling on or before November 29, 1976. Comments will be considered and if the text is revised, it will be published in a subsequent notice. Comments may also be made on the physician labeling.

I. SCOPE

Various notices published in the FEDERAL REGISTER as part of the Drug Efficacy Study Implementation (DESI) project have covered specific estrogens. These include: DESI 740 (36 FR 21537, November 10, 1971; 38 FR 26824, September 26, 1973; 40 FR 8242, February 26, 1975; 40 FR 32774, August 4, 1975); DESI 1543 (37 FR 14826; July 25, 1972); DESI 2238 (37 FR 15028; July 27, 1972); DESI 7661 (37 FR 18225; September 8, 1972). The drug products in these notices were classified as effective for one or more indications.

In addition, other notices are published elsewhere in this issue of the FEDERAL REGISTER giving the Administration's findings concerning the effectiveness of numerous estrogenic drug products and stating specific indications for which those products are effective. (See DESI 1543 (Docket No. 76N–0356); DESI 2238 (Docket No. 76N–0261); DESI 7661 (Docket No. 76N–0377).)

This notice applies not only to the particular estrogens subject to the Drug Efficacy Study, including products containing estrogens in fixed combination with other drugs (e.g., estrogen-tranquilizer combinations for which hearing requests are under review and which are not referenced above), but to all such products that are the subject of a new drug application approved either before or after the Drug Amendments of 1962 and also to any identical, related, or similar drug product (21 CFR 310.6) whether or not it is the subject of an approved new drug application, with two exceptions. The exceptions are estrogen-progestagen oral contraceptives and oral diethylstilbestrol (DES) products intended for postcoital contraception, which should be labeled according to guidelines provided specifically for those drugs. (21 CFR 310.501).

It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes by writing to the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD–310), 5600 Fishers Lane, Rockville, MD 20852.

The following drug entities, along with their salts and esters, are examples of estrogens which are covered by this notice; however, this is not intended to be an exhaustive listing: Benzestrol, chlorotrianisene, conjugated estrogens, dienestrol, diethylstilbestrol, esterfied estrogens, estradiol, estriol, estrone, ethinyl estradiol, hexestrol, mestranol, methallenestril, piperazine estrone sulfate, polyestradiol phosphate, and promethestrol.

II. BACKGROUND

FDA is charged with assuring that drugs are safe and effective for their intended use and that their labeling provides adequate information for such use and is not false or misleading. The full disclosure of information to physicians concerning such matters as effectiveness, contraindications, warnings, precautions, and adverse reactions is an important element in the discharge of that responsibility. The statutory scheme anticipates that new information concerning the safety and effectiveness of marketed drugs may require that FDA prescribe changes in their labeling to reveal limitations on use or warn of previously unanticipated hazards. Many labeling changes have been effected as a result of the Drug Efficacy Study.

The scientific literature has reported an increased risk of endometrial cancer in postmenopausal women treated with estrogens for long periods. In addition, reports of an association between intrauterine exposure to sex hormones and development of congenital anomalies have appeared, as well as reports of an increased risk of vaginal cancer in adolescent daughters exposed in utero to an estrogen (diethylstilbestrol). A specific warning about the possibility of vaginal cancer has already been required in the labeling of diethylstilbestrol and closely related congeners. (DESI 740, 40 FR 32774, August 4, 1975.) Although similar data are not available for other estrogens, it cannot be presumed that they will not induce the same changes.

These reports showing or suggesting an association between estrogen use and the occurrence of adverse effects generate a need for revision of the labeling to inform physicians of these recent findings. The nature of the findings and the uses of estrogens are such that information should also be furnished to the patient.

Elsewhere in this issue of the FEDERAL REGISTER the Commissioner of Food and Drugs is proposing to amend 21 CFR Part 310 by adding a new § 310.515 that will require patient labeling for all estrogenic drug products for general use. Proposed § 310.515 specifies the kind of information to be contained in the patient labeling, without giving the text of the labeling, and the way in which it is to be made available to the patient. The patient labeling for estrogens is to be based on the approved physician labeling for those drugs.

As a result of the new information, the Food and Drug Administration has undertaken an extensive review of available information about estrogens. In addition, the evidence related to estrogens and endometrial cancer was reviewed by FDA's Obstetrics and Gynecology Advisory Committee at an open meeting held on December 16, 1975. Concluding that there appears to be an increased risk of endometrial cancer associated with long-term estrogen use in postmenopausal women, the Advisory Committee recommended that the labeling be revised to reflect this finding and that patient labeling be developed. A copy of the minutes of that meeting has been placed on file in the office of the Hearing Clerk (HFC–20), Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852 as part of the file on the proposed regulation § 310.515 (Docket No. 76N–0384).

On the basis of the estrogens review, the text of the revised physician labeling and the text for patient labeling are set forth later in this notice. Among the scientific papers reviewed are those listed in the notice of proposed rulemaking to establish a new § 310.515 published elsewhere in this issue of the FEDERAL REGISTER. The references are also cited in the bibliography given in the physician labeling proposed herein.

The Director of the Bureau of Drugs advises that the patient labeling in this notice for estrogen drug products complies with the patient labeling requirements proposed in § 310.515 and can be relied upon by manufacturers, packers, and distributors to meet those requirements.

In the FEDERAL REGISTER of April 7, 1975 (40 FR 15392), the Commissioner proposed new requirements concerning

the content and format of prescription drug labeling. The Director of the Bureau of Drugs concludes that the physician labeling for estrogens for general use is consistent with the proposed prescription drug labeling format. In addition, that notice proposed (§ 1.112(c)(6)(ii)) that printed patient information be referenced under the "Precautions" section of the physician labeling and reprinted at the end of it. The physician labeling set forth here provides for that format to be used when patient labeling is put into use.

III. Comments Solicited

Because of the information that has become available, its impact on manufacturers, physicians, and patients, and the wide usage of estrogens, the Director of the Bureau of Drugs seeks comment on the text of both the full disclosure physician labeling and the patient labeling. Comment as to the appropriateness of the indications for any DESI drug is not sought, as that opportunity has been given in the various notices published to implement the Drug Efficacy Study, including the DESI notices published elsewhere in this issue of the Federal Register and referred to above.

IV. Implementation

Although comment on the labeling is sought, the importance of the new information is such that the revised labeling for physicians should be put into use without delay. Patient labeling may also be used and its use is encouraged, but since the requirement for patient labeling for these drugs is the subject of a rule making procedure, use of such labeling may be delayed until the rule making procedure is completed.

The Food and Drug Administration will regard as misbranded and subject to regulatory action, any estrogen product for general use that is shipped in interstate commerce by manufacturers, repackers, relabelers, or distributors after November 29, 1976 without labeling which is substantially the same in content as the physician labeling set forth in this notice. Such labeling may be put into use in advance of approval or submission of a supplement to a new drug application.

Holders of approved new drug applications for estrogen drug products for general use shall submit supplements on or before November 29, 1976 to provide for the revised physician labeling.

The notice of proposed rule making for patient labeling proposes that that requirement will become effective 60 days after it is published as a final order.

Upon reviewing the comments received on the physician and patient labeling for estrogens, the Director of the Bureau of Drugs will publish a followup DESI notice in the Federal Register applicable not only to DESI drugs but to all estrogens for general use, giving the text of the patient labeling and if necessary on the basis of comments, the text of revised physician labeling. Notwithstanding changes that may appear in the text of patient labeling published after the comment period, such labeling that is already in use and substantially the same in content as the text given below in item VI may continue to be used for 120 days after publication of the final regulation § 310.515.

V. Physician Labeling

The physician labeling for estrogens for general use is set forth below.

ESTROGEN LABELING

Boxed Warning

1. *Estrogens Have Been Reported To Increase The Risk of Endometrial Carcinoma.*

Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.[1-3] This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.[4]

The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment[1] and on estrogen dose.[2] In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;[3] it therefore appears prudent to utilize such a regimen.

Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy.

There is no evidence at present that "natural estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. *Estrogens should not be used during pregnancy.*

The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.[5, 6] This risk has been estimated as not greater than 4 per 1000 exposures.[7] Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis.[8-12] It is not known whether this condition is a precursor of vaginal malignancy. Although similar data are not available with the use of other estrogens, it is reasonable to presume they would induce similar changes.

Several reports suggest an association between intrauterine exposure to female sex hormones and congential anomalies, including congential heart defects and limb reduction defects.[13-15] One case control study[16] estimated a 4.7 fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The estimated rate of these abnormalities in the population from which the cases were obtained was 0.2 abnormalities per 1000 live births in the years 1968–1973. It is not known how many of the 0.2 abnormalities per thousand live births arose in women who were taking sex hormones; therefore 0.2 per 1000 is to some degree an overestimate of the spontaneous rate of these abnormalities. These data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000.

In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestagens are effective for these uses.

If (*name of drug*) is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the possibility of termination of the fetus, and, in light of these risks, of the pregnancy.

(For products containing diethylstilbesterol but not labeled for postcoital contraception, labeling must include before the description section the following statement in block capital letters: THIS DRUG PRODUCT SHOULD NOT BE USED AS A POSTCOITAL CONTRACEPTIVE.[17])

DESCRIPTION

(To be supplied by manufacturer)

(*Description should include the following information.*)

1. The proprietary name and the established name, if any, of the drug product;

2. The type of dosage form and the route of administration to which the labeling applies;

3. The same qualitative and/or quantitative ingredient information as required for labels;

4. If the product is sterile, a statement of that fact;

5. The pharmacological or therapeutic class of the drug product;

6. The chemical name and structural formula. When appropriate, other im-

See footnotes at end of article.

portant chemical or physical information, such as physical constants, pH, etc., should also be included.

CLINICAL PHARMACOLOGY

(To be supplied by the manufacturer)

INDICATIONS

(Depending on the specific drug and dosage form (see DESI notices Nos. 1543, 2238, and 7661 published elsewhere in this issue of the FEDERAL REGISTER for specific indications) the labeling may include appropriate indications from those stated below.)

(*Name of Drug*) is indicated in the treatment of:

1. Moderate to severe *vasomotor* symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.)
2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women, such as those who are more than 5 years postmenopausal with progressing inoperable or radiation-resistant disease, and in men with inoperable disease in whom bilateral orchidectomy is contraindicated.
8. Prostatic carcinoma — palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequnetly, the benefit to be derived from estrogen therapy for this indication must be carefully weighted against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens

(Name of drug) has not been shown to be effective for any purpose during pregnancy and its use may cause severe harm to the fetus (see boxed warning).

Contraindications

Estrogens should not be used in women (or men) with any of the following conditions:

1. Known or suspected cancer of the breast except in appropriately selected patients with progressing inoperable or radiation resistant disease.
2. Known or suspected estrogen-dependent neoplasia.
3. Known or suspected pregnancy (See Boxed Warning).
4. Undiagnosed abnormal genital bleeding.
5. Cerebral vascular or coronary artery disease (except when used in the treatment of breast or prostatic malignancy).
6. Thrombophlebitis or thromboembolic disorders.
7. A past history of thrombophlebitis or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

Warnings

1. *Induction of malignant neoplasms.* Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning).

At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast,[18] although a recent long-term followup of a single physician's practice has raised this possibility.[18a] Because the animal data indicate a need for caution, women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be administered an estrogen with caution and a careful breast examination should be performed.

2. *Gall bladder disease.* A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens,[18] similar to the 2-fold increase previously noted in users of oral contraceptives.[19]

3. *Effects similar to those caused by estrogen-progestagen oral contraceptives.* There are several serious adverse effects of oral contraceptives, most of which have not, up to now, been documented as consequences of postmenopausal estrogen therapy. This may reflect the comparatively low doses of estrogen used in postmenopausal women. It would be expected that the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement are more likely to result in these adverse effects, and, in fact, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement.[20-23]

a. *Thromboembolic disease.* It is now well established that users of oral contraceptives have an increased risk of various thromboembolic and thrombotic diseases, including thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction.[24-31] Cases of retinal thrombosis and optic neuritis have been reported in oral contraceptive users. There is evidence that the risk of several of these adverse reactions is related to the dose of the drug.[32,33] An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives.[34,35] If feasible, estrogen should be discontinued at least 4 weeks before, and not resumed until at least 4 weeks after, surgery of the type associated with an increased risk of thromboembolism.

Although to date no increased rate of thromboembolic and thrombotic disease in postmenopausal users of estrogens has been detected[18,36] this does not rule out the possibility that such an increase may be present or that subgroups of women who have underlying risk factors or who are receiving larger doses of estrogen may have an increased risk. Therefore estrogens should not be used in persons with thromboembolic disorders and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use or in patients with cerebral vascular or coronary artery disease.

Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men[37] to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When estrogen doses of this size are used, any of the thromboembolic and thrombotic adverse effects associated with oral contraceptive use should be considered a clear risk.

b. *Hepatic adenoma.* Benign hepatic adenomas appear to be associated with the use of oral contraceptives.[38-40] Although benign, and rare, these may rupture and cause death through intraabdominal hemorrhage. Such lesions have not yet been reported in association with other estrogen or progestagen preparations but should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has also been reported in women taking estrogen-containing oral contraceptives.[39] The relationship of this malignancy to these drugs is not known at this time.

c. *Elevated blood pressure.* Increased blood pressure is not uncommon in women using oral contraceptives. There is now evidence that this occurs with use of estrogens in the menopause[41] and blood pressure should be monitored with estrogen use, especially if high doses are used.

d. *Glucose tolerance.* A worsening of glucose tolerance has been observed in a significant percentage of patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed while receiving estrogen.

4. *Hypercalcemia.* Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases. If this occurs, the drug should be stopped and appropriate measures taken to reduce the serum calcium level.

Precautions

A. General Precautions.

1. A complete medical and family history should be taken prior to the initiation of any estrogen therapy. The pretreatment and periodic physical examinations should include special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed.

2. Fluid retention—Because estrogens may cause some degree of fluid retention,

See footnotes at end of article.

conditions which might be influenced by this factor such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation.

3. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc.

4. Oral contraceptives appear to be associated with an increased incidence of mental depression. Although it is not clear whether this is due to the estrogenic or progestagenic component of the contraceptive, patients with a history of depression should be carefully observed.

5. Preexisting uterine fibromyomata may increase in size while using estrogen.

6. The pathologist should be advised of estrogen therapy when relevant specimens are submitted.

7. Patients with a past history of jaundice during pregnancy have an increased risk of recurrence of jaundice while receiving estrogen-containing oral contraceptive therapy. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated.

8. Estrogens may be poorly metabolized in patients with impaired liver function and they should be administered with caution in such patients.

9. Because estrogens influence the metabolism of calcium and phosphorus, they should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency.

10. Because of the effects of estrogens on epiphyseal closure, they should be used judiciously in young patients in whom bone growth is not complete.

11. Certain endocrine and liver function tests may be affected by estrogen-containing oral contraceptives. The following similar changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

B. (Insert the following when patient labeling is required or used in advance of a requirement.) Information for the Patient. See text of Patient Package Insert which is attached below.

C. Pregnancy Category X (Pregnancy category designations and labeling statements are set forth in 40 FR 15392–15399). See Contraindications and Boxed Warning.

D. Nursing Mothers. It is not known whether this drug is excreted in human milk. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Adverse Reactions

(See Warnings regarding induction of neoplasia, adverse effects on the fetus, increased incidence of gall bladder disease, and adverse effects similar to those of oral contraceptives, including thromboembolism.) The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives:

1. *Genitourinary system.*
Breakthrough bleeding, spotting, change in menstrual flow.
Dysmenorrhea.
Premenstrual-like syndrome.
Amenorrhea during and after treatment.
Increase in size of uterine fibromyomata.
Vaginal candidiasis.
Change in cervical eversion and in degree of cervical secretion.
Cystitis-like syndrome.

2. *Breast.*
Tenderness, enlargement, secretion

3. *Gastrointestinal.*
Nausea, vomiting.
Abdominal cramps, bloating.
Cholestatic jaundice.

4. *Skin.*
Chloasma or melasma which may persist when drug is discontinued.
Erythema multiforme.
Erythema nodosum.
Hemorrhagic eruption.
Loss of scalp hair.
Hirsutism.

5. *Eyes.*
Steepening of corneal curvature.
Intolerance to contact lenses.

6. *CNS.*
Headache, migraine, dizziness.
Mental depression.
Chorea.

7. *Miscellaneous.*
Increase or decrease in weight.
Reduced carbohydrate tolerance.
Aggravation of porphyria.
Edema.
Changes in libido.

Overdosage

Serious ill effects have not been reported following the ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration

1. *Given cyclically for short term use only:*

For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., 3 weeks on and 1 week off).

Attempts to discontinue or taper medication should be made at 3 to 6 month intervals.

The usual dosage range is *(to be supplied by manufacturer)*.

2. *Given cyclically:*
Female hypogonadism.
Female castration.
Primary ovarian failure.
(Dosage to be inserted.)

3. *Given for a few days:*
Prevention of postpartum breast engorgement.
(Dosage to be inserted.)

4. *Given chronically:*
Inoperable progressing prostatic cancer. (Dosage to be inserted).

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women. (See indications) (Dosage to be inserted.)

Treated patients with an intact uterus sholud be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

References

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VI. Patient Labeling

The proposed patient package labeling for estrogens for general use is set forth below.

WHAT YOU SHOULD KNOW ABOUT ESTROGENS

Estrogens are female hormones produced by the ovaries. The ovaries make several different kinds of estrogens. In addition, scientists have been able to make a variety of synthetic estrogens. As far as we know, all these estrogens have the same properties and therefore much the same usefulness, side effects, and risks. This leaflet is intended to help you understand what estrogens are used for, the risks involved in their use, and how to use them as safely as possible.

This leaflet includes the most important information about estrogens, but not all the information. If you want to know more, you can ask your doctor or pharmacist to let you read the package insert prepared for the doctor.

USES OF ESTROGEN

Estrogens are prescribed by doctors for a number of purposes, including:

1. To provide estrogen during a period of adjustment when a woman's ovaries no longer produce it, in order to prevent certain uncomfortable symptoms of estrogen deficiency. (All women normally stop producing estrogens, generally between the ages of 45–50; this is called the menopause.)

2. To prevent symptoms of estrogen deficiency when a woman's ovaries have been removed surgically before the natural menopause.

3. To prevent pregnancy. (Estrogens are given along with a progestagen, another female hormone; these combinations are called oral contraceptives or birth control pills. Patient labeling is available to women taking oral contraceptives and they will not be discussed in this leaflet.)

4. To treat certain cancers in men (cancer of the prostate or breast) and in women (certain cancers of the breast when they occur more than 5 years after menopause).

5. To prevent painful swelling of the breasts after pregnancy in women who choose not to nurse their babies.

THERE IS NO PROPER USE OF ESTROGENS IN A PREGNANT WOMAN.

ESTROGENS IN THE MENOPAUSE

In the natural course of their lives, all women eventually experience a fall in estrogen production. This usually occurs between ages 45 and 50 but may occur earlier or later. Sometimes the ovaries may need to be removed before natural menopause by an operation, producing a "surgical menopause."

When the amount of estrogen in the blood begins to decrease many women may develop typical symptoms: Feelings of warmth in the face, neck, and chest or sudden intense episodes of heat and sweating throughout the body (called "hot flashes" or "hot flushes"). These symptoms are sometimes very uncomfortable. A few women eventually develop changes in the vagina (called "atrophic vaginitis") which cause discomfort, especially during intercourse.

Estrogens can be prescribed to treat these symptoms of the menopause. It is estimated that considerably more than half of all women undergoing the menopause have only mild symptoms or no symptoms at all and therefore do not need estrogens. Other women may need estrogens for a few months, while their bodies adjust to lower estrogen levels. Sometimes the need will be for periods longer than six months. In an attempt to avoid over-stimulation of the uterus (womb), estrogens are usually given cyclically during each month of use, that is, three weeks of pills followed by one week without pills.

Sometimes women experience nervous symptoms or depression during menopause. There is no evidence that estrogens are effective for such symptoms and they should not be used to treat them, although other treatment may be needed.

You may have heard that taking estrogens for long periods (years) after the menopause will keep your skin soft and supple and keep you feeling young.

There is no evidence that this is so, however, and such long-term treatment carries important risks.

ESTROGENS TO PREVENT SWELLING OF THE BREASTS AFTER PREGNANCY

If you do not breast feed your baby after delivery, your breasts may fill up with milk and become painful and engorged. This usually begins about 3 to 4 days after delivery and may last for a few days to up to a week or more. Sometimes the discomfort is severe, but usually it is not and can be controlled by pain relieving drugs such as aspirin and by binding the breasts up tightly. Estrogens can be used to try to prevent the breasts from filling up. While this treatment is often successful, in many cases the breasts fill up to some degree in spite of treatment. The dose of estrogens needed to prevent pain and swelling of the breasts is much larger than the dose needed to treat symptoms of the menopause and this may increase your chances of developing blood clots in the legs or lungs (see below). Therefore, it is important that you discuss the benefits and the risks of estrogen use with your doctor if you have decided not to breast feed your baby.

THE DANGERS OF ESTROGENS

1. *Cancer of the uterus.* If estrogens are used in the postmenopausal period for more than a year, there is an increased risk of *endometrial cancer* (cancer of the uterus). Women taking estrogens have roughly 5 to 10 times as great a chance of getting this cancer as women who take no estrogens. To put this another way, while a postmenopausal woman not taking estrogens has one chance in a 1,000 each year of getting cancer of the uterus, a woman taking estrogens has one chance in 100 to 200 each year. For this reason *it is important to take estrogens only when you really need them.*

The risk of this cancer is greater the longer estrogens are used and also seems to be greater when larger doses are taken. For this reason *it is important to take the lowest dose of estrogen that will control symptoms and to take it only as long as it is needed.* If estrogens are needed for longer periods of time, your doctor will want to reevaluate your need for estrogens at least every six months.

Women using estrogens should report any irregular vaginal bleeding to their doctors; such bleeding may be of no importance, but it can be an early warning of cancer of the uterus. If you have undiagnosed vaginal bleeding, you should not use estrogens until a diagnosis is made and you are certain there is no cancer of the uterus.

2. *Other possible cancers.* Estrogens can cause development of other tumors in animals, such as tumors of the breast, cervix, vagina, or liver, when given for a long time. At present there is no good evidence that women using estrogens in the menopause have an increased risk of such tumors, but there is no way yet to be sure they do not. This is a further reason to use estrogens only when clearly needed. While you are taking estrogens, it is important that you go to your doctor at least once a year to check on your uterus, cervix, vagina, and breasts. Also, if members of your family have had breast cancer or if you have breast nodules or abnormal mammograms (breast x-rays), your doctor will want to carry out especially careful examination of your breasts.

3. *Gall bladder disease.* Women who use estrogens after menopause are about 2½ times as likely to develop gall bladder disease needing surgery as women who do not use estrogens. Birth control pils have a similar effect.

4. *Abnormal blood clotting.* Oral contraceptives increase the risk of blood clotting in various parts of the body. This can result in a stroke (if the clot is in the brain), a heart attack (clot in a blood vessel of the heart), or a pulmonary embolus (a clot which forms in the legs or pelvis, then breaks off and travels to the lungs). Any of these can be fatal.

At this time use of estrogens in the menopause is not known to cause such blood clotting, but this has not been fully studied and there could still prove to be such a risk. It is recommended that if you have had a heart attack, angina, or stroke, or if you have had clotting in the legs or lungs associated with use of estrogens or birth control pills, you should not use estrogens (unless they are being used to treat cancer of the breast or prostate).

The larger doses of estrogen used to prevent swelling of the breasts after pregnancy have been reported to cause clotting in the legs and lungs.

SPECIAL WARNING ABOUT PREGNANCY

You should not receive estrogen if you are pregnant, but pregnant women sometimes do get estrogen anyway. If this occurs, there is a greater than usual chance that the developing child will be born with a birth defect, although the possibility remains fairly small. If the child is a female, she has an increased risk of developing cancer of the vagina or cervix later in life (in the teens or twenties). Every possible effort should be made to avoid exposure to estrogens during pregnancy. If exposure occurs, see your doctor.

OTHER EFFECTS OF ESTROGENS

In addition to the serious known risks of estrogens described above, estrogens have the following side effects and potential risks:

1. *Nausea and vomiting.* The most common side effect of estrogen therapy is nausea. Vomiting is less common.

2. *Effects on breasts.* Estrogens may cause breast tenderness or enlargement and may cause the breasts to secrete a liquid. These effects are not dangerous.

3. *Effects on the uterus.* Estrogens may cause benign fibroid tumors of the uterus to get larger.

Some women will have menstrual bleeding when estrogens are stopped for one week each month. But if the bleeding occurs on days you are still taking estrogens you should report this to your doctor.

4. *Effects on liver.* Women taking oral contraceptives develop on rare occasions a benign tumor of the liver which can rupture and bleed into the abdomen. So far, these tumors have not been reported in women using estrogens in the menopause, but you should report any swelling or unusual pain of tenderness in the abdomen to your doctor immediately.

Women with a past history of jaundice (yellowing of the skin and white parts of the eyes) may get jaundice again during estrogen use. If this occurs, stop taking estrogens and see your doctor.

5. *Mental depression.* A few women develop depression while on estrogen therapy. If you have had depression in the past, it may reappear or get worse during estrogen therapy. If you do become severely depressed, stop taking estrogens and call your doctor.

6. *Other effects.* Estrogens may cause excess fluid to be retained in the body. This may make some conditions worse, such as epilepsy, migraine, heart disease, or kidney disease.

A spotty darkening of the skin can develop, particularly in the face, and may persist.

SUMMARY

Estrogens have important uses, but they have serious risks as well. You must decide, with your doctor, whether the risks are acceptable to you in view of the benefits of treatment. Except where your doctor has prescribed estrogens for use in special cases of cancer of the breast or prostate, you should not use estrogens if you have cancer of the breast or uterus, are pregnant, have undiagnosed abnormal vaginal bleeding, clotting in the legs or lungs, or have had a stroke, heart attack or angina, or clotting in the legs or lungs in the past while taking estrogens.

You can help your doctor prescribe estrogens as safely as possible by understanding that he will require regular physical examinations while you are taking them and will try to discontinue the drug as soon as he can and use the smallest dose possible. Be alert for signs of trouble including:

1. Abnormal bleeding from the vagina.
2. Pains in the calves or chest or sudden shortness of breath, or coughing blood (indicating possible clots in the legs, heart, or lungs).
3. Severe headache, dizziness, faintness, or changes in vision (indicating possible developing clots in the brain or eye).
4. Breast lumps (you should ask your doctor how to examine your own breasts).
5. Jaundice (yellowing of the skin).
6. Mental depression.

HOW SUPPLIED; DOSAGE AND ADMINISTRATION

(A description of the particular product, instructions on dosage and administration to be supplied by manufacturer.)

Interested persons may, on or before November 29, 1976 submit to the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, written comments (prefer-

ably in quintuplicate and identified with the Hearing Clerk docket number found in brackets in the heading of this document) regarding the physician labeling and the patient labeling. Received comments may be seen in the above office during working hours Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.31) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: September 17, 1976.

J. RICHARD CROUT,
Director, Bureau of Drugs.

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federal register

WEDNESDAY, SEPTEMBER 29, 1976

PART IX:

CONSUMER PRODUCT SAFETY COMMISSION

■

PROCEDURES FOR PETITIONING FOR RULEMAKING UNDER SECTION 10 OF THE CONSUMER PRODUCT SAFETY ACT

Interim Rules

Title 16—Commercial Practices

CHAPTER II—CONSUMER PRODUCT SAFETY COMMISSION

PART 1110—PROCEDURES FOR PETITIONING FOR RULEMAKING UNDER SECTION 10 OF THE CONSUMER PRODUCT SAFETY ACT

Interim Rules

• *Purpose.* The purpose of this document is to establish interim procedures (16 CFR Part 1110) governing the submission and disposition of petitions for the issuance, amendment, or revocation of consumer product safety rules filed with the Consumer Product Safety Commission under section 10 of the Consumer Product Safety Act (CPSA) (15 U.S.C. 2059). Although these procedures become effective as interim procedures upon publication in the FEDERAL REGISTER, the Commission seeks public comment on the procedures.•

These procedures apply only to petitions filed under section 10 of the Consumer Product Safety Act. Requests for the consideration of rulemaking matters under the Consumer Product Safety Act which do not involve consumer product safety rules are not required to comply with these procedures. However, persons filing such requests are encouraged to follow as closely as possible the requirements and recommendations for filing petitions under section 10 of the CPSA as set forth in § 1110.7 of this part.

Petitions regarding products regulated under the other acts administered by the Commission: the Flammable Fabrics Act (15 U.S.C. 1191 et seq.), the Federal Hazardous Substances Act (15 U.S.C. 1261 et seq.), the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 et seq.), or the Refrigerator Safety Act (15 U.S.C. 1211 et seq.) are governed by the Administrative Procedure Act (5 U.S.C. 553 (e)) and, where applicable, existing Commission procedures at 16 CFR 1607.14, 16 CFR 1500.82, 16 CFR 1500.201, and 21 CFR 2.65. However, persons filing such petitions are encouraged to follow as closely as possible the requirements and recommendations for filing petitions under section 10 of the CPSA as set forth in § 1110.7 of this part.

Section 10 of the Consumer Product Safety Act provides that "any interested person, including a consumer or consumer organization, may petition the Commission to commence a proceeding for the issuance, amendment, or revocation of a consumer product safety rule." As defined in section 3(a)(2) of the CPSA, a "consumer product safety rule" is either a consumer product safety standard described in section 7(a) of the act or a rule under section 8 of the act declaring a consumer product a banned hazardous product.

A "consumer product safety standard," as described in section 7(a) of the CPSA, consists of one or more of the following types of requirements: (i) "Requirements as to performance, composition, contents, design, construction, finish, or packaging of a consumer product," or (ii) "requirements that a consumer product be marked with or accompanied by clear and adequate warnings or instructions or requirements respecting the form of warnings or instructions." A consumer product safety standard is issued by the Commission pursuant to the procedures set forth in sections 7 and 9 of the act and regulations issued under those sections of the act (16 CFR Part 1105; 16 CFR Part 1109).

A "banned hazardous product" as described in section 8 of the act is a consumer product which is being, or will be, distributed in commerce and which presents an unreasonable risk of injury for which no feasible consumer product safety standard under the CPSA would adequately protect the public. The Commission may declare a product a banned hazardous product under the procedures of section 8 and 9 of the act.

Before commencing a proceeding to promulgate or materially amend a consumer product safety rule under sections 7, 8, and 9 of the CPSA, the Commission must preliminarily determine that the product presents an unreasonable risk of injury, that the rule is reasonably necessary to eliminate or reduce an unreasonable risk of injury associated with such product and, in the case of a rule declaring the product a banned hazardous product, that no feasible consumer product safety standard under the act would adequately protect the public from the unreasonable risk of injury associated with such product.

Before commencing a proceeding to revoke a consumer product safety rule, the Commission, under section 9(e) of the act, must find a change in circumstances such that consumers are no longer exposed to an unreasonable risk of injury associated with a consumer product or that a rule is no longer necessary to eliminate or reduce an unreasonable risk of injury associated with a consumer product.

Section 10 of the CPSA further provides that within 120 days after a person or group files a petition for issuance, amendment or revocation of a consumer product safety rule, "the Commission shall either grant or deny the petition * * *. If the Commission denies such petition it shall publish in the FEDERAL REGISTER its reasons for such denial." If the Commission grants such petition, it must promptly commence an appropriate proceeding under section 7 or 8 of the CPSA (or section 9 in the case of a revocation or minor modification of a rule).

Since the CPSA does not specify the reasons the Commission must use in deciding whether or not to grant petitions, the Commission believes that in addition to establishing procedures for the treatment of petitions, the Commission should also describe in this document the major factors it considers in deciding petitions. These factors, including specific information relevant to these factors, are based on the language of the act, the legislative history, and other consideration relevant to effectuating the purpose of the act. They are enumerated below in § 1110.11.

As to any petition filed under section 10 after October 27, 1975, if the Commission denies the petition or if it fails to grant or deny the petition within 120 days, the petitioner may commence a civil action in a United States district court to compel the Commission to initiate the action requested.

Section 10(e)(2) of the act provides that if the petitioner can demonstrate to the satisfaction of the court, by a preponderance of the evidence in a de novo proceeding before the court, that the consumer product presents an unreasonable risk of injury, and that failure of the Commission to initiate a rulemaking proceeding under section 7 or 8 unreasonably exposes the petitioner or other consumers to a risk of injury presented by the consumer product, the court shall order the Commission to initiate the action requested by the petitioner.[1]

Petitions under the CPSA which request action other than issuance, amendment, or revocation of consumer product safety rules do not fall within section 10 and therefore are not subject to the 120-day rule (examples of such petitions include requests for the issuance of regulations governing the notification to the Commission of information regarding "new consumer products" under section 13 of the act or requests for the issuance of regulations with respect to conflicts of interest by members of the Commission).

Consideration of petitions under section 10 involves a very extensive process within the Commission. Engineers, biomedical scientists, economists, lawyers, epidemiologists, and other professionals on the staff analyze petitions and, based on a review of this staff analysis, the Commission decides whether to grant or deny the petition. Because the effort involved with petitions is extensive, the Commission believes it appropriate to take reasonable steps to ensure that it treats as petitions only those documents which can fairly be considered to be petitions, yet not discourage petitioning by imposing overly technical requirements.

The Commission receives thousands of communications every year. Many of these are intended to warn of product safety problems encountered by the writer or caller, others make suggestions and many simply ask for information. In considering the application of this policy to these communications, the Commission believes that a fair and reasonable approach is to consider as petitions only those written documents which contain the following information:

1. Facts, such as personal experience; medical, engineering or injury data; or a research study, which it is claimed establish that a consumer product safety rule (a standard or a ban) or an amendment or revocation thereof is necessary; and

2. An explicit request to initiate the suggested rulemaking, including a brief

[1] Although the act does not expressly so provide, it is assumed that the court's findings would be different if the petition requests revocation or modification so as to make the rule less stringent.

description of the substance of the consumer product safety rule, or amendment or revocation of the rule, which the petitioner seeks.

Communications received by the Commission that are not considered to be petitions are evaluated even though they are not processed in the same manner as petitions. For example, letters of complaint or reports of injuries may lead to a "substantial product hazard" action under section 15 of the CPSA to require the manufacturer, distributor, or retailer to inform the public of a hazardous product and/or repair, replace or refund the purchase price of the product. Should a complaint about a product lead the Commission to conclude that the product presents an imminent and unreasonable risk of death, serious illness, or severe personal injury, the Commission has the authority under section 12 of the CPSA to file an action in the appropriate United States district court to declare the product to be an "imminent hazard" and have it removed from the marketplace.

In deciding whether to treat a document as a petition, the Commission will consider the substance and not the form of the document. The fact that a document clearly details a safety problem and requests a specific Commission rule and yet does not contain the word "petition" will not cause the Commission to refuse to consider it as a petition.

CONCLUSION AND PROPOSAL

The Commission concludes that guidance is needed immediately for the preparation and processing of petitions under section 10 of the CPSA. The continued absence of procedural rules could lead to confusion and unnecessary expenditure of resources by everyone involved. Accordingly, these rules, effective September 29, 1976, shall serve as interim rules to govern the submission and processing of section 10 petitions.

Because these rules are rules of agency practice and procedure the Administrative Procedure Act requirements for notice of proposed rulemaking, opportunity for public participation and delayed effective date are not applicable. Even if the rules were to be considered general rulemaking, the Commission for good cause finds that such notice and public procedure and a delayed effective date are impracticable and not in the public interest because guidance is needed immediately to avoid confusion or unnecessary expenditure of resources.

However, the Commission believes that the public should be afforded the opportunity to comment upon these interim rules. Accordingly, these rules will be published in the proposed rules section of the FEDERAL REGISTER to facilitate and encourage public comment.[1] The public should be assured that any and all comments received upon these rules will be carefully considered by the Commission in its decision as to what form the final rules for section 10 petitions should take. Active and enlightened public comment on rules such as these is the major vehicle by which the Commission is informed of the public's beliefs and desires as to how this agency should discharge its statutory duties.

Accordingly, pursuant to provisions of the Consumer Product Safety Act (sec. 10, Pub. L. 92-573, 86 Stat. 1217; 15 U.S.C. 2059), the Commission establishes as interim rules and proposes the following new Part 1110 of Title 16, Chapter II, Subchapter B:

Sec.

AUTHORITY: Sec. 10, Pub. L. 92-573, 86 Stat. 1217; 15 U.S.C. 2059.

§ 1110.1 Policy considerations.

(a) Among the most important activities carried out by the Consumer Product Safety Commission (CPSC) is the issuance of consumer product safety rules (standards or bans), under sections 7, 8, and 9 of the Consumer Product Safety Act (CPSA) (15 U.S.C. 2056-2058).

(b) To most effectively carry out its mission with respect to the establishment of effective and sound consumer product safety rules, the Commission must have the interest and involvement of the public to the fullest possible extent.

(c) One of the most effective ways to involve the public in the establishment of consumer product safety rules is through the public's right to petition the Commission for such rules. Accordingly, prompt attention and thorough consideration should be given by the Commission to all documents that purport to be petitions.

(d) In deciding whether a document is a petition under section 10 of the act, the Commission will be concerned more with the substance than the form of the document. For example, the fact that a document clearly details a safety problem and requests a specific consumer product safety rule and yet is not labeled as a "petition" shall not in itself lead the Commission to refuse to consider it as a petition. On the other hand, the Commission will not treat a communication as a petition unless it appears the party responsible for the communication expresses an intent that it be so regarded.

§ 1110.2 Scope.

(a) This part establishes procedures for the submission and disposition of petitions for the issuance, amendment or revocation of a consumer product safety rule filed under section 10 of the Consumer Product Safety Act (15 U.S.C. 2059).

(b) Requests for the consideration of rulemaking matters under the Consumer Product Safety Act which do not involve consumer product safety rules are not required to comply with these procedures (for example, requests for issuance of interpretative rules, or changes in CPSC rules of procedure, or practice). However, persons filing such requests are encouraged to follow as closely as possible the requirements and recommendations for filing petitions under section 10 of the CPSA as set forth in § 1110.7. In considering petitions under the CPSA that do not involve issuance, amendment, or revocation of consumer product safety rules, the Commission shall not be obligated to comply with the requirements for petitions set forth in section 10 of the act.

(c) Petitions regarding products regulated under the Federal Hazardous Substances Act (FHSA) (15 U.S.C. 1261 et seq.), the Flammable Fabrics Act (FFA) (15 U.S.C. 1191 et seq.), the Poison Prevention Packaging Act of 1970 (PPPA) (15 U.S.C. 1471 et seq.), and the Refrigerator Safety Act (15 U.S.C. 1211, et seq.) are governed by the Administrative Procedure Act (5 U.S.C. 553(e)) and, where applicable, existing Commission procedures at 16 CFR 1607.14, 16 CFR 1500.82, 16 CFR 1500.201, and 21 CFR 2.65. Persons filing such petitions, however, are encouraged to follow as closely as possible the requirements and recommendations for filing petitions under section 10 of the CPSA as set forth in § 1110.7.

§ 1110.3 Definitions.

For the purposes of this Part

(a) "Act" or "CPSA" means the Consumer Product Safety Act (15 U.S.C. 2051 et seq.), as amended by Pub. L. 94-284 (May 11, 1976).

(b) "Commission" means the Consumer Product Safety Commission, established by section 4 of the Consumer Product Safety Act (15 U.S.C. 2053).

(c) "Consumer product" means a product as defined in section 3(a)(1) of the Consumer Product Safety Act (15 U.S.C. 2052(a)(1)).

(d) "Consumer product safety rule" means (1) a consumer product safety standard described in section 7(a) of the act or (2) a rule under section 8 of the act declaring a consumer product a banned hazardous product.

(e) "Consumer product safety standard", means a standard under section 7 (a) of the CPSA consisting of one or more of the following types of requirements: (1) Requirements as to performance, composition, contents, design, construction, finish, or packaging of a consumer product, or (2) requirements that a consumer product be marked with or accompanied by clear and adequate warnings or instructions or requirements respecting the form of warnings or instructions. A standard is issued by the Commission pursuant to the procedures set out in sections 7 and 9 of the act and regulations issued under those sections of the act (16 CFR Part 1105; 16 CFR Part 1109).

[1] EDITORIAL NOTE: Since these interim rules are effective on September 29, 1976, they are published in the rules section of this issue.

(f) "Banned hazardous product" means a consumer product which has been declared by the Commission by rule in accordance with sections 8 and 9 of the act to be a banned hazardous product on the basis of a finding that the product will be distributed in commerce and that it presents an unreasonable risk of injury for which no feasible consumer product safety standard under the CPSA would adequately protect the public.

(g) "Petition" under section 10 of the act means a written document which requests the issuance, amendment, or revocation of a consumer product safety rule and which complies with the provisions of § 1110.7(a).

§ 1110.4 General.

Any person, including a consumer or consumer organization, may file with the Commission a petition requesting the Commission to commence a proceeding for the issuance, amendment or revocation of a consumer product safety rule (i.e., a consumer product safety standard or a rule declaring a consumer product to be a banned hazardous product).

§ 1110.5 Place of filing.

A petition filed under this part should be mailed to: Office of the Secretary, Consumer Product Safety Commission, Washington, D.C. 20207. Persons wishing to file a petition in person may do so in the Office of the Secretary.

§ 1110.6 Time of filing.

For purposes of computing time periods under this part, a petition shall be considered filed when time-date stamped by the Office of the Secretary. A document is time-date stamped when it is received in the Office of the Secretary.

§ 1110.7 Requirements and recommendations for petitions.

(a) *Requirements.* To be considered a petition under this part, any request for the issuance, amendment or revocation of a consumer product safety rule must meet the requirements of this paragraph (a). A petition filed under this part shall:

(1) Be written in the English language;

(2) Contain the name and address of the petitioner;

(3) Indicate the consumer product (or products) regulated under the Consumer Product Safety Act for which a consumer product safety rule is sought or for which there is an existing consumer product safety rule sought to be modified or revoked;

(4) Set forth facts which establish the claim that the issuance, amendment, or revocation of a consumer product safety rule is necessary (for example, such facts may include personal experience; medical, engineering or injury data; or a research study); and

(5) Contain an explicit request to initiate Commission rulemaking and set forth a brief description of the substance of the proposed consumer product safety rule or amendment or revocation thereof which it is claimed should be issued by the Commission. (A general request for regulatory action which does not reasonably specify the type of action requested shall not be sufficient for purposes of this part.)

(b) *Recommendations.* The Commission encourages the submission of as much information as possible related to the petition. Thus, to assist the Commission in its evaluation of a petition, to the extent the information is known and available to the petitioner, the petitioner is encouraged to supply the following information or any other information relating to the petition. The petition will be considered by the Commission even if the petitioner is unable to supply the information recommended in this paragraph (b). However to the extent possible, the petitioner is encouraged to:

(1) Describe the specific risk(s) of injury to which the petition is addressed, including the degree (severity) and the nature of the risk(s) of injury associated with the consumer product and possible reasons for the existence of the risk of injury (for example, product defect, poor design, faulty workmanship, or intentional or unintentional misuse);

(2) State why a consumer product safety standard would not be feasible if the petitioner requests the issuance of a rule declaring the product to be a banned hazardous product; and

(3) Supply or reference any known documentation, engineering studies, technical studies, reports of injury, medical findings, legal analyses, economic analyses and environmental impact analyses relating to the petition.

(c) *Procedural recommendations.* The following are procedural recommendations to help the Commission in its consideration of petitions. The Commission requests but does not require, that a petition filed under this part:

(1) Be typewritten,

(2) Include the word "petition" in a heading preceding the text,

(3) Specify that it is brought under section 10 of the CPSA,

(4) Include the telephone number of the petitioner, and

(5) Be accompanied by at least five (5) copies of the petition.

§ 1110.8 Documents not considered petitions under section 10 of the CPSA.

(a) A document filed with the Commission which addresses a topic or involves a product outside the jurisdiction of the Commission will not be considered to be a petition. After consultation with the Office of the General Counsel, the Office of the Secretary will forward to the appropriate agency documents which address products or topics within the jurisdiction of other agencies. The Office of the Secretary shall notify the sender of the document that it has been forwarded to the appropriate agency.

(b) A petition filed under the Consumer Product Safety Act which addresses a risk of injury associated with a product which could be eliminated or reduced to a sufficient extent by action taken under the Federal Hazardous Substances Act, the Poison Prevention Packaging Act of 1970, or the Flammable Fabrics Act may be considered by the Commission under those acts. However, if the Commission finds by rule, in accordance with section 30(d) of the CPSA, as amended by Pub. L. 94-284, that it is in the public interest to regulate such risk of injury under the CPSA, it may do so. Upon determination by the Office of the General Counsel that a petition should be considered under one of these acts rather than the CPSA, the Office of the Secretary shall docket and process the petition under the appropriate act and inform the petitioner of this determination. Such docketing, however, shall not preclude the Commission from proceeding to regulate the product under the CPSA at some future time after making the necessary findings.

(c) Any other documents filed with the Office of the Secretary that are determined by the Office of the General Counsel not to be petitions under section 10 of the CPSA shall be evaluated for possible staff action. The Office of the Secretary shall notify the writer of the manner in which the Commission staff is treating the document. If the writer has indicated an intention to petition the Commission, the writer shall be informed by the Office of the Secretary of the procedure to be followed for petitioning.

§ 1110.9 Statement in support of or in opposition to petitions; Duty of petitioners to remain apprised of developments regarding petitions.

(a) Any person may file a statement with the Office of the Secretary in support of or in opposition to a petition prior to Commission action on the petition. Persons submitting statements in opposition to a petition are encouraged to provide copies of such statements to the petitioner.

(b) It is the duty of the petitioner, or any person submitting a statement in support of or in opposition to a petition, to keep himself or herself apprised of developments regarding the petition. Information regarding the status of petitions is available from the Office of the Secretary of the Commission.

(c) The Office of the Secretary shall send to the petitioner a copy of the staff briefing package on his or her petition at the same time the package is transmitted to the Commissioners for decision.

§ 1110.10 Public hearings on petitions.

(a) Under section 10(c) of the act the Commission may hold a public hearing or may conduct such investigation or proceeding, including a public meeting, as it deems appropriate to determine whether a petition should be granted.

(b) If the Commission decides that a public hearing or meeting on a petition, or any portion thereof, would contribute to its determination of whether to grant or deny the petition, it may issue a public notice of a hearing or meeting on the petition and invite interested persons to submit their views through an oral or written presentation or both. All such proceedings will be conducted in accordance with the Commission's Policy on Meetings: Advance Public Notice, Public Attendance, and Recordkeeping (16 CFR

Part 1012). The hearings or meetings shall be informal, nonadversary, legislative-type proceedings.

§ 1110.11 Factors the Commission considers in granting or denying petitions.

(a) The major factors the Commission considers in deciding whether to grant or deny a petition under section 10 include the following items:

(1) Whether the consumer product involved presents an unreasonable risk of injury.

(2) Whether a consumer product safety rule is reasonably necessary to eliminate or reduce the risk of injury.

(3) Whether failure of the Commission to initiate the rulemaking proceeding requested would unreasonably expose the petitioner or other consumers to the risk of injury which the petitioner alleges is presented by the product.

(4) Whether, in the case of a petition to declare a consumer product a "banned hazardous product" under section 8 of the act, the product is being or will be distributed in commerce and whether a feasible consumer product safety standard would adequately protect the public from the unreasonable risk of injury associated with such product.

(b) In considering these factors, the Commission will treat as an important component of each one the relative priority of the risk of injury associated with the product about which the petition has been filed and the Commission's resources available for rulemaking activities with respect to that risk of injury. The CPSC Policy on Establishing Priorities for Commission Action, 16 CFR 1009.8, published July 8, 1976 (41 FR 27960) sets forth the criteria upon which Commission priorities are based. These criteria, briefly summarized, with respect to petitions under this policy, are as follows:

(1) Frequency and severity of injuries associated with a consumer product.

(2) Causality of injuries.

(3) Potential for a consumer product to cause chronic illness and injuries which do not become evident until some time after use of exposure to the product.

(4) Potential impact of Commission regulatory action in terms of possible reduction of injuries and increased cost to both producers and consumers, as well as potential effect on the usefulness and availability of the product.

(5) Nature of the risk of injury in terms of its forseeability by the consumer.

(6) Special vulnerability of children, elderly, and handicapped consumers to the risk of injury presented.

(7) Probability of injury to the consumer taking into consideration such things as the number of units in use, frequency of use, and likelihood of exposure to the identified risk of injury during typical use.

(8) Any additional criteria which would lead the Commission to treat a petition as high priority matter.

§ 1110.12 Granting of petitions.

(a) Section 10(d) of the act provides that within 120 days after the filing of a petition under section 10 of the act, the Commission shall either grant or deny the petition. The Commission may also grant a petition in part or deny it in part. If the Commission grants a petition, it shall promptly commence proceedings for the issuance, amendment or revocation of a consumer product safety standard under the appropriate provisions of sections 7, 8, or 9 of the act.

(b) The granting of a petition requesting a consumer product safety rule and the commencing of a proceeding does not necessarily mean that the rule requested will be issued. If the Commission grants a petition and commences a proceeding for a consumer product safety rule under section 7 or 8 of the CPSA, it may subsequently find it necessary to withdraw the proceeding pursuant to section 7(f) or section 9(a)(1)(B) of the act. A decision as to the issuance, amendment, or revocation of a rule must be made on the basis of all available information developed in the course of the rulemaking proceeding, including information obtained during the period for comment provided under section 9 of the CPSA (15 U.S.C. 2058). Should later information indicate that the action is unwarranted or not necessary, the Commission may terminate the proceeding.

§ 1110.13 Denial of petitions.

(a) If the Commission denies a petition brought under section 10 of the CPSA, it shall publish in the FEDERAL REGISTER its reasons for such denial.

(b) The denial of a petition shall be without prejudice to the petitioner to refile if the petitioner can demonstrate that new or changed circumstances or additional information justify reconsideration by the Commission.

(c) A Commission denial of a petition shall not preclude the Commission from continuing to consider matters raised in the petition.

Interested persons are invited to submit on or before December 28, 1976, written comments regarding this document. Comments received after this date will be considered to the extent practicable.

Comments should be submitted, preferably in 5 copies, addressed to the Secretary, Consumer Product Safety Commission, Washington, D.C. 20207. Received comments may be seen in the Office of the Secretary, Washington, D.C. during working hours Monday through Friday.

Dated: September 24, 1976.

SADYE E. DUNN,
Secretary, Consumer Product Safety Commission.

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