

Any person who will be adversely affected by the foregoing order may, at any time on or before May 2, 1983, submit to the Dockets Management Branch (address above) written objection thereto. Objections shall show how the person filing will be adversely affected by the order, specify with particularity the provisions of the order deemed objectionable, and state the grounds for the objections. Objections shall be filed in accordance with requirements of 21 CFR 71.30. If a hearing is requested, the objections shall state the issue for the hearing and shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Three copies of all documents shall be filed and shall be identified with the docket number found in brackets in the heading of this document. Any objections received in response to the order may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the provisions of the Federal Food, Drug, and Cosmetic Act (sec. 706(b) (c), and (d), 74 Stat. 399-403 (21 U.S.C. 376(b), (c), and (d)) and the transitional provisions of the Color Additive Amendments of 1960 (Title II, Pub. L. 86-618, sec. 203, 74 Stat. 404-407 (21 U.S.C. 376 note)) and under the authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10).

Dated: March 28, 1983.

William F. Randolph,
Acting Associate Commissioner for
Regulatory Affairs.

[FR Doc. 83-9419 Filed 3-29-83; 11:13 am]
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[Docket No. 82N-0064]

Plasma Derived From Therapeutic Plasma Exchange

AGENCY: Food and Drug Administration.
ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is advising interested persons that plasma derived from therapeutic plasma exchange is a biological product subject to the licensing requirements of section 351(a) of the Public Health Service Act.

FOR FURTHER INFORMATION CONTACT: Joseph Wilczek, National Center for Drugs and Biologics (HFN-813), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301-443-1306.

SUPPLEMENTARY INFORMATION:

Therapeutic plasma exchange is a medical procedure by which a patient's plasma is incrementally removed and replaced with electrolyte and/or protein solutions. The procedure (also known as therapeutic plasmapheresis) is intended to remove harmful elements from a patient's blood.

Patients undergoing therapeutic plasma exchange may suffer from any of a number of disorders, such as paraproteinemic conditions, idiopathic thrombocytopenic purpura, kidney disease, or other disorders that may be caused by agents in the blood that transmit disease.

Plasma obtained from a patient during therapeutic plasma exchange is known as therapeutic exchange plasma (TEP). TEP may contain certain rare antibodies that are not available from any other source. Because TEP obtained during therapeutic plasma exchange is potentially hazardous to human health, FDA believes that use of TEP should be limited to further manufacture of special in vitro diagnostic reagents, such as Anti-Nuclear Antibody, Rheumatoid Factor, Anti-DNA, or other products, when such use of the source material is approved by the Director, Office of Biologics, National Center for Drugs and Biologics, FDA.

FDA has found that certain persons are shipping TEP in interstate commerce to manufacturers of in vitro diagnostic devices without first obtaining a product license for TEP from the Office of Biologics, FDA. FDA also has learned that these persons and others are unaware that TEP is a biological product subject to the licensing requirements of section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)). The agency therefore concluded that it is important to inform all interested persons of the regulatory status of TEP.

FDA advises that TEP offered for sale, barter, or exchange in interstate commerce is a biological product subject to the licensing requirements of section 351(a) of the Public Health Service Act (42 U.S.C. 262(a)). Accordingly, any person who intends to collect and ship TEP in interstate commerce must first obtain a product license from FDA. A licensed manufacturer of Source Plasma (Human) must obtain a separate product license for production of TEP and must amend its establishment license to cover collection and shipment of TEP, if necessary. Because TEP is a blood product, a manufacturer of TEP is subject to the requirements of the current good manufacturing practice regulations for blood and blood components in 21 CFR Part 606. In addition, when TEP is shipped in

interstate commerce and intended for use in an in vitro diagnostic device, it is also considered a device component, subject to regulation under the medical device provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 through 392). Further, as provided in 21 CFR 606.110(b) of the biologics regulations, plasmapheresis of donors who do not meet the donor requirements of 21 CFR 640.63, 640.64, and 640.65 for the collection of plasma containing rare antibodies shall be permitted only with the prior approval of the Director, Office of Biologics. Such an FDA approval is made as part of the license approval for the manufacture or shipment of TEP.

Therapeutic plasma exchange is a medical procedure to be used at the discretion of a licensed physician and is not regulated by FDA. Therefore, a product license from FDA is required only when the TEP that is collected during the therapeutic plasma exchange is intended or offered for sale, barter, or exchange in interstate commerce.

Dated: March 24, 1983.

Mark Novitch,
Deputy Commissioner of Food and Drugs.

[FR Doc. 83-9424 Filed 3-31-83; 8:45 am]
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[Docket No. 82N-0009; DESI Nos. 8867 and 9296]

Professional Labeling for Reserpine Drugs; Revised Labeling

AGENCY: Food and Drug Administration.
ACTION: Notice.

SUMMARY: This notice requires that a precaution statement be included in professional labeling of reserpine-containing drugs, stating that these drugs cause tumors in mice and rats.

DATES: Revised labeling to be used on or before September 1, 1983. Supplements to approved NDA's and ANDA's due on or before May 31, 1983. The revised labeling may be used without advance approval by FDA.

ADDRESSES: Communications in response to this notice should be identified with Docket No. 82N-0009, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Supplements to full new drug applications (identify with NDA number); Division of Cardio-Renal Drug Products (HFN-110), Rm. 16B-45, National Center for Drugs and Biologics.
Supplements to abbreviated new drug applications (identify with ANDA

number); Division of Generic Drug Monographs (HFN-530), National Center for Drugs and Biologics.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFN-310), National Center for Drugs and Biologics.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFN-501), National Center for Drugs and Biologics.

FOR FURTHER INFORMATION CONTACT:

Jean Patterson, National Center for Drugs and Biologics (HFN-8), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (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. Informing physicians about necessary precautions is an important element in fulfilling that responsibility. The statutory scheme anticipates that new information on the safety and effectiveness of marketed drugs may require that FDA prescribe labeling changes to reveal limitations of use or to warn of previously unanticipated hazards.

Accordingly, the Director of the National Center for Drugs and Biologics has reviewed available data and concludes that a precaution statement should be added to the professional labeling of drug products containing reserpine. The statement is needed to inform physicians and other health professionals that animal carcinogenicity studies in rodents have shown reserpine to be a rodent tumorigen, causing an increased incidence of mammary fibroadenomas in female mice, malignant tumors of the seminal vesicles in male mice, and malignant adrenal medullary tumors in male rats. The breast neoplasms are thought to be related to reserpine's prolactin-elevating effect. This action is being taken under the National Center's continuing review of the relationship between the use of drugs that elevate prolactin levels and mammary carcinogenesis. (A notice requiring precautionary statements in the labeling of certain neuroleptic drugs was published in the *Federal Register* of August 8, 1980 (45 FR 52931), and amended on September 8, 1981 (46 FR 44886)).

The issue of whether reserpine is tumorigenic has been considered by several advisory committees. An Ad Hoc Committee on Reserpine and Breast

Cancer was appointed by FDA to evaluate all available data from animal, laboratory, clinical, and epidemiological studies suggesting that the use of reserpine increases the risk of breast cancer. In June 1978 the Committee issued a summary statement that the possibility of an underlying causal relationship between reserpine use and breast cancer could not be rejected. They stated: "The lack of consistency of the findings between studies of differing designs, the inconsistent findings of a dose-response relationship, the relatively low order of magnitude of the risk ratio, and the absence of a currently defensible biological rationale are all factors operating against an etiologic interpretation. However, while the risk ratio is of a relatively low order of magnitude, it is not inconsequential, at least half the studies looking for a dose response relationship found some evidence to support its existence, and there is some uniformity across studies with respect to an association with 'recent use'."

The FDA Toxicology Advisory Committee's Report on Antipsychotic Drugs stated that all prolactin-elevating drugs are considered to have carcinogenic potential for the mammary glands in rats and mice. These conclusions were published in the *Federal Register* of May 16, 1978 (43 FR 21051).

At the June 22, 1979, and November 20, 1979 meetings of FDA's Cardiovascular and Renal Drugs Advisory Committee, data were also presented and discussed from animal carcinogenicity studies conducted for the National Cancer Institute. These studies, in which reserpine was administered to rodents for 2 years, showed treatment-related increases in the incidence of mammary fibroadenomas, malignant tumors of the seminal vesicles, and malignant adrenal medullary tumors.

Proposed labeling revisions for reserpine-containing products were reviewed by the Cardiovascular and Renal Drugs Advisory Committee at their February 22, 1980 meeting. The revision required by this notice reflects their advice.

References

1. Summary Statement of the FDA Ad Hoc Committee on Reserpine and Breast Cancer, June 1978.
2. FDA Toxicology Advisory Committee Report on Antipsychotic Drugs, August 12, 1977.
3. Transcript of the Cardiovascular and Renal Drugs Advisory Committee, June 22, 1979.

4. Minutes of the Cardiovascular and Renal Drugs Advisory Committee, November 19-20, 1979.

5. Minutes of the Cardiovascular and Renal Drugs Advisory Committee, February 22, 1980.

Copies of the above references have been placed in the file on Doc. No. 82N-0009 in the Dockets Management Branch (HFA-305), Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen between 9 a.m. and 4 p.m., Monday through Friday.

In view of these findings, the Director of the National Center for Drugs and Biologics concludes that the labeling for all drug products containing reserpine should contain a precaution statement on the possible adverse effects of the elevated serum prolactin levels and on animal carcinogenicity associated with administration of these drugs. Accordingly, manufacturers of these drug products shall revise the professional labeling to add the following text to the Precautions section after the existing paragraph:

Animal tumorigenicity: rodent studies have shown that reserpine is an animal tumorigen, causing an increased incidence of mammary fibroadenomas in female mice, malignant tumors of the seminal vesicles in male mice, and malignant adrenal medullary tumors in male rats. These findings arose in 2 year studies in which the drug was administered in the feed at concentrations of 5 and 10 ppm—about 100 to 300 times the usual human dose. The breast neoplasms are thought to be related to reserpine's prolactin-elevating effect. Several other prolactin-elevating drugs have also been associated with an increased incidence of mammary neoplasia in rodents.

The extent to which these findings indicate a risk to humans is uncertain. Tissue culture experiments show that about one-third of human breast tumors are prolactin-dependent *in vitro*, a factor of considerable importance if the use of the drug is contemplated in a patient with previously detected breast cancer. The possibility of an increased risk of breast cancer in reserpine users has been studied extensively; however, no firm conclusion has emerged. Although a few epidemiologic studies have suggested a slightly increased risk (less than twofold in all studies except one) in women who have used reserpine, other studies of generally similar design have not confirmed this. Epidemiologic studies conducted using other drugs (neuroleptic agents) that, like reserpine, increase prolactin levels and therefore would be considered rodent mammary carcinogens, have not shown an

association between chronic administration of the drug and human mammary tumorigenesis. While long-term clinical observation has not suggested such an association, the available evidence is considered too limited to be conclusive at this time. An association of reserpine intake with pheochromocytoma or tumors of the seminal vesicles has not been explored.

This notice applies to all single-entity and combination reserpine-containing drug products that are the subject of approved new drug applications and also to any identical, related, or similar drug product that contains reserpine (21 CFR 310.6), whether or not it is the subject of an approved new drug application. Any person may request an opinion of the applicability of this notice to a specific drug product the person manufactures or distributes by writing to the Division of Drug Labeling compliance (address given above).

Supplements to approved NDA's or ANDA's providing for appropriate revision of labeling to add the above precaution statement shall be submitted on or before May 31, 1983. Applicants shall put the revised labeling into use by September 1, 1983. The revised labeling may be used without advance approval by the Food and Drug Administration under the provisions of 21 CFR 314.8(d).

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 201(n), 502, 505, 52 Stat. 1041, 1050-1053, as amended (21 U.S.C. 321(n), 352, 355)) and under the authority delegated to the Director of the National Center for Drugs and Biologics (21 CFR 5.70).

Dated: March 25, 1983.

Harry M. Meyer, Jr.,
Director, National Center for Drugs and Biologics.

[FR Doc. 83-8422 Filed 3-31-83; 8:45 am]

BILLING CODE 4160-01-M

[Docket No. 80N-0295]

Clarification of Policy; Over-the-Counter Drug Review

AGENCY: Food and Drug Administration.
ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is clarifying its policy on placing "feedback" communications in the administrative records of appropriate over-the-counter (OTC) drug rulemaking proceeding.

DATE: Comments by May 31, 1983.

ADDRESS: Written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, National Center for Drugs and Biologics (HFN-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the *Federal Register* of September 29, 1981 (46 FR 47740), FDA published a policy statement concerning (1) the submission and review of proposed protocols to evaluate an ingredient or condition in the OTC drug review, (2) meetings with industry or other interested persons, (3) communications by the agency on submissions of test data and other information, and (4) maintenance of a public record involving these activities.

The policy statement explained that "feedback" information provided by FDA to manufacturers on Category II or III conditions would be placed on public file in the Dockets Management Branch (address above) and be available to all interested persons. However, these communications would not be included in the administrative record for the related OTC drug rulemaking proceeding unless the communication directly influenced an agency decision on a particular matter in the rulemaking or provided the substantiation for the agency's decision on that matter. For example, the results of a study that were communicated to the agency in response to "feedback" would be included in the administrative record of a particular OTC drug rulemaking proceeding if the study was relied upon by the agency in reaching a decision on the status of an ingredient covered by that rulemaking.

Questions have arisen concerning the mechanism by which "feedback" material is included in the administrative record of an OTC drug rulemaking proceeding, for example, whether "feedback" material is included in the appropriate rulemaking only in response to a petition by an interested party. The agency advises that when such material directly influences or is used by the agency in reaching a decision on a matter in an OTC drug rulemaking proceeding, the agency will add it to the administrative record prior to publication of the applicable document without the submission of a formal petition by an interested party. Appropriate reference to the material will be included in the relevant proposed rule or final rule document.

Any "feedback" communication that is submitted before a proposed rule is published, but which is not used by the agency in preparing the proposed rule, will be placed in the administrative record when it is opened during the comment period following publication of

the proposed rule. As provided in 21 CFR 330.10(a)(7), following publication of a proposed rule, the administrative record is open 60 days for comments or objections, 12 months for the submission of new data and information, and an additional 60 days for reply comments on the new data and information. "Feedback" communications that occur after the usual closing of the administrative record following publication of the proposed rule, and which are not relied upon or used by the agency in developing the final rule, will remain part of the public record; however, these communications will not be added to the administrative record unless the agency subsequently determines in response to a petition that they should be.

Notice and comments are not necessary before issuing this clarification. (See 5 U.S.C. 553(b)(B).) Furthermore, the purpose and major aspects of this policy statement were described in the preamble to the May 13, 1980 proposed rule on the agency's Category III regulations (45 FR 31422) and in the "feedback" policy statement of September 29, 1981 (46 FR 47740).

Interested persons may, on or before May 31, 1983, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this clarification. Three copies of any comment are to be submitted, except that individuals may submit one copy. Comments are to be identified with Docket No. 80N-0295. Such comments will be considered in determining whether amendments or revisions to the clarification are warranted. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 24, 1983.

Mark Novitch,
Deputy Commissioner of Food and Drugs.

[FR Doc. 83-8423 Filed 3-31-83; 8:45 am]

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Health Resources and Services Administration

Advisory Committee; Meeting

In accordance with section 10(a)(2) of the Federal Advisory Committee Act (Pub. L. 92-463), announcement is made of the following National Advisory body scheduled to meet during the month of June 1983:

Name: Material and Child Health Research Grants Review Committee.

Date and Time: June 9-10, 1983, 9:00 a.m.-5:00 p.m.