

NOTICES

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for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical,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 hearing, he shall file (1) on or before January 10, 1977, a written notice of appearance and request for hearing, and (2) on or before February 8, 1977, 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 6343, 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 Surgical-Dental Drug Products (HFD-100), Rm. 18B-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-30), 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-501), 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: December 1, 1976.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc 76-36044 Filed 12-9-76; 8:45 am]

[Docket No. 76N-0052]

OVER-THE-COUNTER DRUGS

Decision On Theophylline As A Single Ingredient

The Food and Drug Administration (FDA) announces that, as a result of additional information, the Commissioner of Food and Drugs disagrees with the recommendation of the Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Panel ("the Panel") to allow theophylline to be made available over-the-counter (OTC) as a single ingredient. Any OTC drug product containing theophylline as a single ingredient is subject to immediate regulatory action.

In a notice published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38312), FDA proposed to establish conditions under which OTC cold, cough, allergy, bronchodilator, and antiasthmatic

drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Panel. The preamble to the proposal also included the complete conclusions and recommendations of the Panel.

The Panel's recommendations, and the proposed monograph, included its conclusion that several ingredients were safe and effective for OTC use that previously had been limited to prescription use or had been classified for OTC use at a dosage level lower than that recommended by the Panel. After reviewing those specific ingredients, the Commissioner made an initial determination not to disagree with the Panel's recommendations on the OTC use of a number of ingredients, including the use of theophylline as a single ingredient in OTC drug products. The Panel recommended that the adult daily dosage be 100 to 200 milligrams (mg) every 6 hours, not to exceed 800 mg in 24 hours.

The Commissioner stated, however, that although he did not challenge the judgment of the Panel regarding the safety of theophylline, he believed that there was a scientific issue as to whether the recommended dosage levels were therapeutically effective for a significant, identifiable population of asthmatics. Therefore, the Commissioner noted that theophylline was currently undergoing extensive review within the agency and, consequently, the Panel's recommendation might be subject to modification in the tentative final monograph.

Since publication of the Panel's recommendation, the Commissioner has received additional information that requires him to disagree at this time with the Panel's recommendation that theophylline be made available for use as a single ingredient in OTC drug products. This additional information, which was not available during the Panel's deliberations, indicates that the recommended therapeutic dose may be toxic to some individuals. This information suggests that the safe and effective use of this drug requires careful dosage titration based on theophylline serum concentrations.

In a recent report by Miles Weinberger, M.D. and Leslie Hendeles, Ph.D., "Pharmacotherapy of Asthma," "The Journal of the Maine Medical Association," 67:9, 255-266, September 1976, the authors reported the relationship between theophylline dosage and the likelihood of achieving both therapeutic effect and toxicity. The report states that at the median effective dose (50th percentile) of 26 milligrams per kilogram per day (mg/kg/day) in 4 divided doses for children (or 1000 mg/day in 4 divided doses for adults), about 25 percent of the patient population is likely to be at risk of toxicity. The report shows that at the upper adult dosage recommended by the Panel, i.e., 800 mg/day, about 40 percent of the patient population will achieve a therapeutic effect; however, about 25 percent is likely to be at risk of toxicity. At the lower adult dosage recommended by the Panel, i.e., 400 mg/day, the report shows that none of the patient population is likely to be at risk of

toxicity; however, only about 5 percent will achieve a therapeutic effect.

The report notes that current data suggest that theophylline is effective for suppressing chronic asthmatic symptoms when administered in dosages that achieve the therapeutic serum concentration range of 10 to 20 micrograms per milliliter ($\mu\text{g}/\text{ml}$). The Panel stated that studies indicate that variations between patients in their maintenance dose requirements are attributable to remarkable differences in the rate at which theophylline is metabolized. Because of variations in metabolism, about 20 percent of the adult patients receiving 800 mg/day will have theophylline serum concentrations of over 20 $\mu\text{g}/\text{ml}$ and be at risk of toxicity. Drs. Weinberger and Hendeles recommend that, because serious toxicity such as seizures and death can occur from excessive serum concentrations (generally over 40 $\mu\text{g}/\text{ml}$) without earlier signs of lesser toxicity, clinical titration should be based on measurement of theophylline serum levels. A copy of this report has been placed on file in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20857 and may be seen between the hours of 9 a.m. and 4 p.m., Monday through Friday.

Because of this additional information suggesting careful titration based on measurement of theophylline serum levels, the Commissioner concludes that, pending publication of the tentative final monograph, theophylline should not be made available as a single ingredient in OTC drug products. Therefore, he is stating his disagreement with the Panel's recommendation regarding the OTC use of theophylline as a single ingredient. This action will in effect limit the use of theophylline as a single ingredient to prescription drug products. This was the status of such use prior to publication of the Panel's recommendations. The Commissioner believes that, because of the additional information, it is only prudent to maintain the existing status of the use of theophylline as a single ingredient; he also believes that allowing the use of theophylline to increase, pending publication of the tentative final monograph, is unwarranted.

The Commissioner advises that the use of theophylline, both as a single ingredient and in combination, and both in prescription and OTC drug products, is undergoing extensive review in FDA. Therefore, conditions under which theophylline is used may be subject to additional changes in the future. The Commissioner recommends that there not be any proliferation in the number of products containing theophylline, pending the announcement of the results of the review by FDA.

For the above reasons, the Commissioner does not at this time agree with the Panel's recommendation that theophylline be classified in Category I and be made available for OTC use as a single ingredient. Therefore, in accordance with § 330.13(b)(2), (21 CFR 330.13(b)(2)) setting forth the status of ingredients recommended for OTC use under the

OTC drug review, published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580), any product marketed containing theophylline as a single ingredient for OTC use is subject to immediate regulatory action.

Dated: December 3, 1976.

SHERWIN GARDNER,
Acting Commissioner of
Food and Drugs.

[FR Doc. 76-36045 Filed 13-3-76; 3:57 pm]

Office of Education

RESEARCH PROJECTS IN VOCATIONAL EDUCATION

Closing Date for Receipt of Applications for Fiscal Year 1977

Notice is hereby given, pursuant to the authority contained in section 131(a) of Part C of the Vocational Education Act of 1963, as amended (20 U.S.C. 1281(a)), that applications are being accepted for vocational education research project grants and contracts.

Applications must be received by the U.S. Office of Education Application Control Center on or before February 14, 1977.

A. *Applications sent by mail.* An application sent by mail should be addressed as follows: U.S. Office of Education, Application Control Center, Washington, D.C. 20202, Attention: 13.498. An application sent by mail will be considered to be received on time by the Application Control Center if:

(1) The application was sent by registered or certified mail not later than February 9, 1977 as evidenced by the U.S. Postal Service postmark on the wrapper or envelope, or on the original receipt from the U.S. Postal Service; or

(2) The application is received on or before the closing date by either the Department of Health, Education, and Welfare, or the U.S. Office of Education mail room in Washington, D.C. In establishing the date of receipt, the Commissioner will rely on the time-date stamp of such mail rooms or other documentary evidence of receipt maintained by the Department of Health, Education, and Welfare, or the U.S. Office of Education.

B. *Hand delivered applications.* An application to be hand delivered must be taken to the U.S. Office of Education Application Control Center, Room 5673, Regional Office Building Three, 7th and D Streets, SW., Washington, D.C. 20202. Hand delivered applications will be accepted daily between the hours of 8:00 a.m. and 4:00 p.m. Washington, D.C. time, except Saturdays, Sundays, or Federal holidays. Applications will not be accepted after 4:00 p.m. on the closing date.

C. *Program application information.* (1) Applications must be prepared and submitted in accordance with instructions and forms which may be obtained from the Division of Research and Demonstration, Bureau of Occupational and Adult Education, Office of Education, Room 5018, 7th and D Streets, SW., Washington, D.C. 20202.

(2) To be eligible for review by the Office of Education, an application from a local educational agency must be approved by the State board. In order to permit the consideration of an application for funding from a local educational agency by the Office of Education, the approval of the State board with respect to that application should be received by the Office of Education with the application by the deadline established above. In those instances where State boards do not convene prior to the deadline date for receipt of applications, the applications must contain a statement indicating when the board will convene to consider the application, and a statement indicating the date when the recommendation of the State board will be received in the Office of Education. The recommendation by the State board may not be received by the Vocational Education Research Program more than 50 calendar days after the closing date for receipt of applications. All applications from other than local educational agencies must be submitted in accordance with 45 CFR 103.13(a) of the program regulations (20 U.S.C. 1281(a)).

(3) *Duplication.* In order to assure that applications do not duplicate projects already undertaken in the State, the applicant shall (1) Send a copy of the application to the State Director of Vocational Education, and (2) notify the Commissioner of Education of this action by attaching a copy of the letter that transmitted the application to the State Director of Vocational Education to each copy of the application transmitted to the Office of Education.

The State Director may advise the Commissioner of Education of applications considered to be a duplication of other projects in the State, within 30 days of receipt of the application. An application may only be considered to be a duplication of effort, if the objectives, and procedures of the application are closely related to the objectives, and procedures of completed or on-going projects. A letter that indicates a duplication of effort should document how the objectives, and procedures are so similar that funding would not be warranted.

(4) It is anticipated that grants and assistance contracts will be awarded in each of the eight priority areas listed in the additional criteria for selection of applicants for Fiscal Year 1977. The eight priority areas are: (a) Equal access and opportunity, (b) Sex-role stereotyping and sex bias, (c) Education and work programs, (d) adult and postsecondary vocational education, (e) curriculum management and instructional materials, (f) Personnel development for vocational education, (g) Comprehensive systems of guidance, counseling, placement, and follow-through, and (h) Administration of vocational education at the State and local levels. It is anticipated that approximately 85 new awards will be made for new projects in Fiscal Year 1977. Due to the State allotment system, the size of the award will vary from State to State. The highest ranked application or applications irrespective