[Docket No. 76-0483]

PARKE, DAVIS & CO.

Benylin Expectorant; Opportunity for Hearing On Proposal To Deny Approval of Supplemental New Drug Application

The Food and Drug Administration (FDA) is proposing to deny approval of a supplemental new drug application (NDA 6-514; S-007) for the over-the-counter (OTC) marketing of Benylin Expectorant as an antitussive on the grounds that it has not been shown to be safe for OTC distribution and has not been shown to be effective for use as an antitussive. Parke, Davis & Co., the holder of the new drug application (NDA) for Benylin Expectorant, has until January 3, 1976, to submit a request for hearing in accordance with § 314.200 (21 CFR 314.200). Such request should be identified with the Hearing Clerk docket number found in brackets in the heading of this notice.

Benylin Expectorant is a liquid preparation containing, among other ingredients, diphenhydramine hydrochloride, ammonium chloride, sodium citrate, and menthol. The NDA for Benylin Expectorant was approved in 1948, with indications for use in the treatment of cough due to colds and other congestive symptoms associated with colds.

Although the labeling submitted in the NDA was intended to permit OTC distribution by Benylin Expectorant, the NDA was not approved until revised labeling was submitted restricting the product to prescription use.

In 1957, at the instance of Parke, Davis & Co., in a notice of proposed rulemaking published in the FEDERAL REGISTER of November 27, 1957 (22 FR 9483), FDA proposed revised labeling that would have permitted OTC distribution of diphenhydramine hydrochloride preparations in oral, liquid dosage form. In response to the proposal, Parke, Davis & Co. reconsidered its position and opposed the revised labeling, with the observation that "this product cannot be considered as safe for over-the-counter dispensing, either with or without the suggested changes in labeling." Several other comments on the proposal also opposed OTC status for diphenhydramine hydrochloride preparations. Accordingly, in a notice published in the FEDERAL REGISTER of March 22, 1958 (23 FR 1936), the prescription limitation was retained. Later, in 1969, the firm submitted a supplemental NDA providing for OTC use of Benylin, but withdrew that supplemental NDA in 1970.

In 1964, Parke, Davis & Co. submitted a supplemental NDA, one purpose of which was to obtain approval for inclusion of an antitussive indication in the labeling of Benylin Expectorant. In 1965, FDA advised the firm that the indication was approvable, and, in 1966, approved new labeling that included the antitussive indication.

In a notice published in the FEDERAL REGISTER of July 9, 1966 (31 FR 9426) in connection with the Drug Efficacy Study of the National Academy of Sciences-National Research Council (NAS-NRC), FDA issued a call for data on the effectiveness of all drugs that had been approved pursuant to the new drug procedures from 1938 to October 10, 1962. In 1968, FDA advised Parke, Davis & Co. that a supplemental NDA for Benylin Expectorant providing for revised labeling would not be approved, pending receipt and study of the NAS-NRC report; FDA stated that the supplemental NDA "is approvable when a determination is made that there is substantial evidence of effectiveness of the drug for all of the purposes claimed in the labeling."

On the basis of the NAS-NRC report on antihistamine preparations, FDA, in a notice published in the FEDERAL REGISTER of June 18, 1971 (36 FR 11758), classified diphenhydramine—the principal active ingredient in Benylin Expectorant—as "effective" or "probably effective" for various allergy and sleep-inducing claims, as "possibly effective" for spasmodic bronchial cough, and as "lacking substantial evidence of effectiveness" for other indications, including "antitussive action." In a notice published in the FEDERAL REGISTER of February 9, 1972 (38 FR 4006), FDA announced its conclusion that there was a lack of substantial evidence of the effectiveness of Benylin Expectorant and certain other products as fixed combinations for the indications in their labeling, and offered an opportunity for hearing on its proposal to withdraw approval of the NDA's for those products. By letter of March 9, 1973, Parke, Davis & Co. requested a hearing on the proposed withdrawal of approval of the NDA for Benylin Expectorant.

Among other factors cited by the firm in support of its request for hearing was the submission it had filed for review by the Advisory Review Panel on OTC Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drugs (CCABA Panel). The CCABA Panel had been established as part of the FAD program for review of all OTC drugs in relation to the 1962 effectiveness amendments to the Federal Food, Drug, and Cosmetic Act. The procedures for the OTC Drug Review were published in the FEDERAL REGISTER of May 11, 1972 (37 FR 9464); the call for data to be submitted to the CCABA Panel was published in the FEDERAL REGISTER of August 9, 1972 (37 FR 16029). Parke, Davis & Co. stated in its request for hearing that it considered its submission to the OTC Panel to be a supplement to the NDA for Benylin Expectorant.

Parke, Davis & Co. also responded to the notice of opportunity for hearing by filing revised labeling as part of a supplemental NDA for Benylin Expectorant. The supplemental NDA, submitted by letter of March 22, 1973, provided for changing the name of the product to "Benylin Cough Syrup," for deletion of all ingredients but diphenyldramine hydrochloride from the list of active ingredients (but not from the product formulation), for a change in the description of the product's mechanism of action, and for a modification of the indications for which the product was recommended. The firm observed that the revised labeling provided for prescription use of Benylin "as an alternative to the preferred OTC labeling if FDA finds that Benylin should be continued to be limited to prescription sale."

In a notice published in the FEDERAL REGISTER of May 15, 1973 (38 FR 12769), FDA announced interim guidelines for the formulation and labeling of prescription drugs indicated for cough and allergy. It was stated by FDA that the result of the review of issues concerning the safety and effectiveness of OTC drugs being conducted by the CCABA Panel would have a substantial bearing on the issues surrounding the continued approvability of prescription drugs for relief of cough and allergy. The interim guidelines would therefore govern the status of those prescription drugs until a final monograph was published based on the report of the CCABA Panel.

By letter of November 28, 1973, FDA advised Parke, Davis & Co. that its supplemental NDA providing for revised labeling of Benylin Expectorant as a prescription product did not conform with the interim guidelines and could not be approved. The letter noted that the indication for relief of cough of nonallergic origin could not be approved in the absence of substantial evidence that diphenhydramine hydrochloride is safe and effective for that indication.

In the FEDERAL REGISTER of December 14, 1973 (38 FR 34481), FDA announced that, to assure a consistent policy on both OTC and prescription cough-cold products, the agency would hold in abeyance the interim guidelines announced earlier, and that prescription drugs in the same category as those under review by the CCABA Panel would be permitted to remain on the market with current labeling until a policy for prescription drugs was developed consistent with the OTC monograph for cough-cold products.

By letter of February 5, 1974, Parke, Davis & Co. submitted a supplemental NDA with two clinical studies relating to the effectiveness of Benylin as an antitussive. By letter of November 25, 1974, Parke, Davis & Co. submitted a supplemental NDA with revised labeling providing for OTC use of Benylin as an antitussive, the supplemental NDA that is the subject of this notice. By letter of March 11, 1975, FDA acknowledged receipt of both supplemental NDA's and indicated that no action would be taken pending completion of the review by the CCABA Panel of the data before it. In a letter of March 18, 1975, Parke, Davis & Co. was informed, in response to its inquiry made to the FDA Division of OTC Drug Evaluation, that OTC marketing of Benylin would be unlikely to be subject to regulatory action under the enforcement policy in effect at that time concerning new OTC products. Thereafter, Parke, Davis & Co. commenced OTC marketing of Benylin as Benylin

Cough Syrup with indications for use as an antitussive.

In a proposal published in the FEDERAL REGISTER of December 4, 1975 (40 FR 56675), FDA proposed to clarify its enforcement policy to subject to regulatory action drug ingredients intended for OTC marketing that had previously been limited to prescription use and for which OTC use had not been sanctioned by FDA through appropriate procedures. The proposal would have permitted the OTC marketing of products containing such ingredients, however, upon publication of the report of an OTC advisory review panel recommending that the relevant ingredients and indications be classified as generally recognized as safe and effective for OTC use (Category I), so long as the Commissioner of Food and Drugs did not disagree with that recommendation. By letter of March 20, 1976, Parke, Davis & Co. predicted that the CCABA Panel would recommend that diphenhydramine hydrochloride be classified in Category I as an antitussive, and urged that the Commissioner express his tentative agreement with that recommendation when the panel's report was published. Parke, Davis & Co. stated that if the Commissioner disagreed with the recommendation, the firm would consider renewing its earlier request for hearing in connection with any attendant refusal by FDA to approve its supplemental NDA for OTC labeling for Benylin Expectorant.

A final regulation, published in the FEDERAL REGISTER of August 4, 1976 (41 FR 32580) (based on the December 4, 1975 proposal), announced the effectiveness of the modified enforcement policy. The Commissioner's proposal setting forth the report and recommendations of the CCABA Panel was signed on July 30 and published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38312). The CCABA Panel recommended that diphenhydramine hydrochloride be classified in Category I for OTC use both as an antihistamine and as an antitussive. The Commissioner disagreed with the recommendation relating to antihistaminic use of diphenhydramine hydrochloride (and with the panel's recommendations that several other ingredients be similarly classified), but stated that his decision on the recommendation relating to its antitussive use would be made in the context of his ruling on the supplemental NDA filed by Parke, Davis & Co. for OTC marketing of Benylin Expectorant.

By letters dated September 8, 1976, the Bureau of Drugs of FDA notified Parke, Davis & Co., that its supplemental NDA's submitting evidence for the effectiveness of Benylin as an antitussive and labeling for the OTC use of the product were not approvable. Final action on the supplemental NDA relating to the effectiveness of Benylin as an antitussive was deferred pending review of the data generated by the work of the CCABA Panel, as provided in the FEDERAL REGISTER notice of December 14, 1973. The letter noted, however, that the studies submitted to demonstrate the effectiveness of Benylin as an antitussive were inadequate in a number of respects. The supplemental NDA relating to the safety of Benylin for OTC use was denied because of the sedating properties of diphenhydramine hydrochloride and the absence in the proposed labeling of drug interaction and other warnings and contraindications.

By letter of September 17, 1976, Parke, Davis & Co. requested that the supplemental NDA for OTC use of Benylin be filed over protest pursuant to § 314.110 (d) (21 CFR 314.110(d)). Subsequently, representatives of Parke, Davis & Co. met on several occasions with FDA officials to discuss the status of Benylin. On October 21, 1976, Parke, Davis & Co. made a presentation to the Commissioner in support of its contention that Benylin is safe and effective for OTC use as an antitussive, and the Commissioner took the matter under advisement.

The Commissioner has concluded that Benylin cannot at this time be considered generally recognized as safe and effective for OTC use as an antitussive. Elsewhere in this issue of the FEDERAL REGISTER the Commissioner is publishing an announcement that he does not, at this time, accept the CCABA Panel's recommendation that diphenhydramine hydrochloride be classified in Category I for OTC antitussive use. The purpose of this notice is to offer Parke, Davis & Co. an opportunity for hearing on the denial of its supplemental NDA providing for OTC use of Benylin as a new drug.

DISCUSSION

The Commissioner proposes to deny the supplemental NDA for OTC use of Benylin as an antitussive on two grounds:

1. Diphenhydramine hydrochloride causes a level of drowsiness in those who take it that is sufficient to render it unsafe for use except under the supervision of a physician or other practitioner licensed to dispense prescription drugs.

2. The studies submitted to establish the effectiveness of Benylin as an antitussive do not provide substantial evidence of its effectiveness for that use within the meaning of section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)) and § 314.111(a) (5) (21 CFR 314.111(a)(5)).

In its letter requesting filing of its supplemental NDA over protest, Parke, Davis & Co. also requested that the Commissioner issue, under § 314.200 (21 CFR 314.200), a "specific" rather than a "general" notice of the grounds on which he proposed to deny the supplemental NDA.

The Commissioner does not believe that further specification of the basis for his conclusion that diphenhydramine hydrochloride is unsafe for OTC use is appropriate. The Commissioner has reviewed the data and information on the side-effects of this drug. While he is of the view that the soporific effects of diphenhydramine are sufficient to render it unsafe if available OTC, he also believes that the available information is inconclusive and should be developed in a hearing. The Commissioner advises, however, that any request for hearing must comply in all relevant respects with the requirements of § 314.200.

The Commissioner advises that the specific requirements concerning substantial evidence of effectiveness are se[t] forth in § 314.111(a)(5), reference t[o] which renders this a "specific" notice, as that term is used in § 314.200, with respect to the issue of effectiveness. The Commissioner notes that the issue of the effectiveness of Benylin as an antitussive is relevant to his decision to deny the supplemental NDA for OTC use of Benylin: If Benylin is not shown to be effective as an antitussive, the Commissioner cannot conclude that it is safe for widespread OTC distribution when the product has an accompanying potential for inducing drowsiness, which will be magnified by excessive self-administration to achieve the desired effect. The Commissioner also notes that the issue of the effectiveness of Benylin as an OTC product is indistinguishable from the issue of its effectiveness as a prescription product. If the Commissioner finds at the conclusion of this proceeding that there is a lack of substantial evidence of the effectiveness of Benylin as an antitussive for OTC use, he will consider proposing to withdraw the approval of the NDA for Benylin Expectorant for the antitussive indication before completion of the review of data generated by the CCABA Panel proceeding.

If Parke, Davis & Co. elects to avail itself of the opportunity for hearing pursuant to section 505(d) of the act and § 314.200, it must file with the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockvil[le], MD 20857, (1) A written notice of a[p]pearance and request for hearing by January 3, 1976, and (2) The studies on which it relies together with a statement giving data, information, and analyses on which it relies to justify a hearing, as specified in § 314.200, by February 1[...] 1977. A request for hearing may not rest upon mere allegations or denials, but must set forth specific facts showing there is a genuine and substantial issue of fact that requires a hearing. Responses to this notice may be seen in the office of the Hearing Clerk between the hours of [...] a.m. and 4 p.m., Monday through Friday.

If a hearing is requested and is justified by the response to the notice o[f] opportunity for a hearing, the issues wi[ll] be defined, an Administrative Law Judge will be assigned, and a written notice o[f] the time and place at which the hearing will commence will be issued as soon as practicable.

Any hearing will be open to the public. If, however, the Commissioner finds tha[t] portions of the application that serve as [a] basis for such a hearing contain information concerning a method or process that is entitled to protection as a trad[e] secret, the part of the hearing involving such portions will not be public, unless the respondent so specifies.

The Food and Drug Administration has determined that this document does not contain a major proposal requirin[g] preparation of an inflation impact statement under Executive Order 11821 and OMB Circular A-107. A copy of the inflation impact assessment is on file with the Hearing Clerk, Food and Drug Administration.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052 as amended (21 U.S.C. 355)), and under authority delegated to the Commissioner (21 CFR 5.1(a)(1)). (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: November 22, 1976.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc.76-35075 Filed 11-24-76;10:43 am]

Health Resources Administration

COOPERATIVE HEALTH STATISTICS ADVISORY COMMITTEE AND NURSE TRAINING NATIONAL ADVISORY COUNCIL

Notice of 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 bodies scheduled to meet during the month of January 1977:

Name: Cooperative Health Statistics Advisory Committee.
Date and Time: January 13-14, 1977, 9 a.m.
Place: Sheraton-Park Hotel, Wardman Tower, 2660 Woodley Road NW., Washington, D.C. 20008. Open for entire meeting.
Purpose: The Committee represents the interests of the people of the United States in providing advice and guidance to the Secretary and the National Center for Health Statistics on policies and plans in developing a major new national network of integrated or coordinated subsystems of data collections, processing, and analysis over a wide range of questions relating to general health problems of the population, health care resources, and the utilization of health care services.
Agenda: The Committee will discuss health care cost data, quality control for data collection, and structure for the collection of health care utilization data. Reports will be received and reviewed from the Task Forces on: (1) Applied Statistics Training Institute, (2) Meeting Multiple Health Data Needs Through Modification of National and State Statistical Programs, (3) Component Integration and Organizational Structure, (4) Cost-Sharing, and (5) Definitions. In addition, there will be a report from the Data Applications and Research Branch of the Cooperative Health Statistics System. Suggestions for future meeting dates and agenda items will be discussed.

The meeting is open to the public for observation and participation. Anyone wishing to participate, obtain a roster of members, or other relevant information, should contact Mr. James A. Smith, Room 8-21, Parklawn Building, 5600 Fishers Lane, Rockville, Maryland 20857, Telephone (301) 443-1470.

Name: National Advisory Council on Nurse Training.
Date and Time: January 24-26, 1977, 10:30 a.m.
Place: Conference Room 9, Building 31, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20014.
Open January 24, 10:30 a.m.-12:15 p.m.
Closed remainder of meeting.
Purpose: The Council advises the Secretary and Administrator, Health Resources Administration, concerning general regulations and policy matters arising in the administration of the Nurse Training Act of 1971. The Council also performs final review of grant applications for Federal Assistance for nurse training grants, national research service awards, nurse practitioner grants, research project grants, and special projects for the improvement of nurse training, and makes recommendations to the Administrator, HRA.
Agenda: Agenda items for the open portion of the meeting will cover announcements; consideration of minutes of previous meetings; discussion of future meeting dates; and administrative and staff reports. The remainder of the meeting will be closed to the public for the review of grant applications for Federal assistance in accordance with the provisions set forth in section 552(b) (5) and (6), Title 5, U.S. Code and the Determination by the Administrator, Health Resources Administration, pursuant to Public Law 92-463.

Anyone wishing to obtain a roster of members, minutes of meeting, or other relevant information should contact Dr. Mary S. Hill, Room 6C08, Federal Building, 9000 Rockville Pike, Bethesda, Maryland 20014, Telephone (301) 496-6985.

Agenda items are subject to change as priorities dictate.

Dated: November 22, 1976.

JAMES A. WALSH,
Associate Administrator for Operations and Management.

[FR Doc.76-34957 Filed 11-29-76;8:45 am]

Office of Education

LIBRARY RESEARCH AND DEMONSTRATION PROGRAM

Closing Date for Receipt of Applications

Notice is hereby given that pursuant to the authority contained in sections 201, 221, and 223 of Title II, Part B of the Higher Education Act of 1965, as amended (20 U.S.C. 1021, 1031, and 1033), applications are being accepted from institutions of higher education and other public or private agencies, institutions and organizations that are nonprofit for grants for research and demonstration projects relating to the improvement of libraries or the improvement of the training in librarianship. Processing of these applications will be subject to the availability of funds.

Applications must be received by the U.S. Office of Education Application Control Center on or before January 28, 1977.

A. *Applications sent by mail.* An application sent by mail should be addressed as follows: U.S. Office of Education, Applicant Control Center, 400 Maryland Avenue, S.W., Washington, D.C. 20202, Attention: 13.475. An application sent by mail will be considered to be reecived on time by the Application Control Center if:

(1) The application was sent by registered or certified mail not later than January 24, 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 rooms 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. 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 information and forms.* (1) It is anticipated that grants will be awarded in each of the categories specified in 45 CFR 133, that the total amount of funds available for the Library Research and Demonstration Program will be from $1,000,000 to $2,000,000 and that 20 to 30 awards will be made. The average amount of each grant will be from $50,000 to $80,000.

This statement on the availability of funds does not bind the Office of Education to any particular pattern of distribution except as required by the Higher Education Act, applicable regulations, and appropriations. Rather, actual figures may vary widely from those given due to the uncertainties of the appropriation process.

(2) Further information and application forms may be obtained from the Office of Libraries and Learning Resources, Division of Library Programs, Bureau of Elementary and Secondary Education, Regional Office Building Three, 7th and D Streets, SW., Washington, D.C. 20202, Attention: 13.475.

D. *Applicable regulations.* The regulations applicable to this program include the Office of Education General Provisions Regulations (45 CFR Part 100a) and the regulations governing library research and demonstration in the FEDERAL REGISTER of May 17, 1974 at 39 FR 17546 (45 CFR Part 133) and revised in the FEDERAL REGISTER of February 6, 1976, 41 FR 5393.

(20 U.S.C. 1021, 1031, and 1033)

(Catalog of Federal Domestic Assistance Number 13.475, Library Research and Demonstration Program)

Dated: November 22, 1976.

EDWARD AGUIRRE,
Commissioner of Education.

[FR Doc.76-35048 Filed 11-29-76;8:45 am]